



**Toxicity Report No. S.0015656-13, November 2014
Toxicology Portfolio**

Acute and Subacute Oral Toxicity of Periodate in Rats, July–August 2013

Prepared by Emily May Lent and Lee C.B. Crouse

**Toxicology Portfolio
Toxicity Evaluation Program
Army Institute of Public Health**

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14. ABSTRACT <p>Subacute administration of sodium periodate via oral gavage resulted in a cascade of effects that were secondary to kidney toxicity. Decreased mass of ovaries and epididymides and testicular degeneration were observed in sodium periodate groups with signs of kidney toxicity. These groups also exhibited decreased T3 and T4 in the presence of decreased TSH, a pattern associated with uremia. Sodium periodate exposed rats exhibited both activation of the innate immune system and lymphocyte depletion; however, the pattern of effects was more indicative of a stress leukogram. Effects on the thymus and spleen in the absence of adrenal hyperplasia suggest more direct effects on the immune system. Decreased body mass observed in high dose groups was associated with gross and histopathologic findings in the gastrointestinal tract and may be related to effects on absorption. Increased cholesterol was identified as the critical endpoint and was used to derive the BMDL10s of 17.2 and 33.7 mg/kg-day for females and males, respectively.</p>						
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Authors

Emily May Lent and Lee C.B. Crouse

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Army Institute of Public Health
Toxicology Portfolio (MCHB-IP-TEP)
5158 Blackhawk Road
Aberdeen Proving Ground, MD 21010-5403

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Good Laboratory Practice Compliance Statement

The study described in this report was conducted in compliance with Title 40, Code of Federal Regulations (CFR), Part 792, Good Laboratory Practice Standards, except for the following:

1. The test article characterization (purity) was conducted by the manufacturer and it is not known whether the testing was done in compliance with the above regulation.
2. The concentrations of the test article dosing suspensions/solutions for the acute portion of the study were not verified analytically in accordance with Good Laboratory Practice Standards. The accuracy of the data reported is considered sufficient for the purposes of the study.
3. The statistical analyses of the data from the acute portion of the study were conducted by the U.S. Army Public Health Command statisticians. It is not known if these analyses were conducted in accordance with Good Laboratory Practice Standards.

Submitted By:

Study Director:



EMILY MAY LENT
Toxicologist
Toxicity Evaluation Program (TEP)

12 Nov 2014
Date

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PROTOCOL NO. 30-13-06-01
ACUTE AND SUBACUTE ORAL TOXICITY OF PERIODATE IN RATS,
JULY–AUGUST 2013

1 Summary

1.1 Purpose

The objectives of this study were to determine the oral LD₅₀, 95% confidence intervals and slope of the curve for sodium periodate and potassium periodate in the rat and to determine the effects of repetitive oral exposure to sodium periodate in male and female rats.

1.2 Conclusions

The LD₅₀ for potassium periodate was 732 mg/kg for females and 685 mg/kg for males. The LD₅₀ for sodium periodate was 318 mg/kg for females and 741 mg/kg for males. Repeated oral administration of sodium periodate resulted in mortalities after 4 doses at 741 mg/kg-day in males and after 8 doses at 318 and 370 mg/kg-day in females and males, respectively. These mortalities were likely attributable to kidney toxicity, uremia, and a suite of associated effects. Both sexes had demonstrated signs of kidney toxicity including, increased water intake, increased urine output, dilute urine, and blood in the urine in high dose groups. Additionally, blood urea nitrogen (BUN) was highly elevated in males at 185 mg/kg-day and greater. Decreased mass of the ovaries and epididymides and testicular degeneration were observed in sodium periodate groups with signs of kidney toxicity. These groups also exhibited a pattern of decreased thyroid hormones in the presence of decreased rather than the expected increased thyroid stimulating hormone, a pattern associated with uremia. Effects on the immune system associated with kidney disease are characterized by activation of the innate immune system coupled with immune deficiency. Sodium periodate exposed rats exhibited both activation of the innate immune system and lymphocyte depletion; however, the pattern of effects was more indicative of a stress leukogram. Females at 318 mg/kg-day and males at 185 mg/kg-day sodium periodate and greater had neutrophilia and lymphopenia as well as mild monocytosis and eosinopenia, a pattern consistent with a stress leukogram. Additionally, reductions in spleen and thymus mass associated with atrophy were noted in females at 318 mg/kg-day and in males at 185 mg/kg-day and greater. Effects on the thymus and spleen (*i.e.*, decreased mass and atrophy) in the absence of adrenal hyperplasia suggest more direct effects on the immune system. Rats in high sodium periodate dose groups exhibited malnutrition as indicated by decreased body mass. Body mass and food consumption were reduced in females at 318 mg/kg-day and males at 185 mg/kg-day sodium periodate and greater. In addition to being associated with kidney toxicity, body mass effects were associated with gross and histopathologic findings in the gastrointestinal tract (*e.g.*, erosion/ulcer, necrosis, and hemorrhage) and may be related to effects on absorption. Malabsorption likely contributed to body mass decrements as food conversion efficiency was reduced in female rats at 80 mg/kg-day and greater and in males at 185 mg/kg-day. The reproductive and thyroid related endocrine abnormalities appear to be secondary to uremia, whereas immune system impairment and malnutrition may also be due to direct compound toxicity and stress. Additional direct compound toxicity was evident in the liver as increased mass, ALT, and necrosis were noted in high dose sodium periodate groups. Cholesterol levels increased in a dose dependent manner in males in all sodium periodate groups and in females at 40 mg/kg-day and greater. The increase in cholesterol

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may be indicative of hepatotoxicity or may be a secondary indicator of renal toxicity. Increased cholesterol was identified as the critical endpoint in this study based on the dose-related response and was used to derive the BMDL₁₀s of 17.2 and 33.7 mg/kg-day for females and males, respectively.

2 References

See Appendix A for a listing of references.

3 Authority

This study was conducted with funding from the Environmental Acquisition and Logistics Sustainment Program (AMSRD-MSF) (Military Interdepartmental Purchase Request ((MIPR)) number MIPR2GDATHR117). This toxicology study addresses, in part, the environmental safety and occupational health requirements outlined in Army Regulations (AR) 200-1, AR 40-5, and AR 70-1; Department of Defense Instruction 4715.4; and Army Environmental Requirements and Technology Assessments (AERTA) (DA, 2003; b; 2007ba; 2008; DOD, 1996; USAEC, 2009). It was performed as part of an on-going effort by the U.S. Army Environmental Quality Technology (EQT), Ordnance Environmental Program Pollution Prevention Team, to produce safer ordnance. This program is under the direction of the U.S. Army Research, Development, and Engineering Command Environmental Acquisition Logistics & Sustainment Program and EQT Pollution Prevention.

4 Background

Periodates, anions composed of iodine and oxygen, are being developed as alternatives to perchlorates for use as an oxidizer in military incendiary devices (Ball, 2012; Fields, 2012; Moretti et al., 2012). Alternatives to perchlorate are being pursued due to the environmental and health hazards associated with these compounds. The use of perchlorate has been widely scrutinized due to the potential for the compound to cause thyroid dysfunction and developmental abnormalities. Sodium and potassium periodate have been identified as potential replacement incendiary oxidizers that fulfill the pyrotechnic requirements and are presumed, based on structure, to be less toxic than those currently in use. Periodate ions are larger than perchlorate ions, leading munitions developers to speculate that perhaps the ions are too big to interact with thyroid receptors in the same manner as perchlorate (Ball, 2012; Fields, 2012; Moretti et al., 2012). If passed by the sodium-iodide symporter (NIS), however, the ions will bring atomic iodine into the follicular lumen of the thyroid that will then be convertible to thyroid hormones. These theories are not currently supported by experimental data as the toxicity of periodate has not been investigated.

Existing toxicity data on periodate is limited to an intraperitoneal LD₅₀ in mice of 58 mg/kg for sodium periodate (Lewis, 1996) and an oral LD₅₀ of 7.07 g/kg for pentacalcium orthoperiodate (PCOP) in fasted male rats (Kuhajek and Andelfinger, 1970). Oral exposure to PCOP caused central nervous system depression, gastrointestinal hemorrhage, hemolysis and renal congestion (Kuhajek and Andelfinger, 1970). Any number of these effects may have been attributable to iodate or iodide as metabolism studies have demonstrated that metaperiodate injected intravenously in rats is quickly reduced to iodate and subsequently to iodide (Anghileri, 1965; Taurog et al., 1966). Due to the rapid reduction of periodate to iodate and iodide, exposure of

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tissues to periodate in the present study may be minimal and may be limited to the gastrointestinal mucosa and liver. Exposure in many tissues may be primarily to iodate and iodide.

The toxicity of iodates and iodides varies greatly with the route of administration and the feeding state of the animal. Potassium iodate was 8.2 times more toxic than potassium iodide when given intraperitoneally to fasted mice; however, this difference was reduced to 1.8 times when given orally to fed mice (Webster et al., 1957). Sodium iodate and potassium iodate had nearly identical acute oral toxicity in mice, with LD₅₀ values of 505 mg/kg and 531 mg/kg, respectively, in fasted animals (Webster et al., 1957). Effects of sodium iodate and potassium iodate exposure included alternate hyperactivity and lassitude, weakness, prostration and dyspnea. Excitability, convulsions and paresis of the hind legs frequently preceded death. Transient increases in gastrointestinal pH and degeneration of parietal cells, hemolytic effects including hemoglobinuria and hemosiderin deposits in the kidneys, and non-specific fatty changes in the viscera were observed. Mortality was attributed to renal damage. Symptoms of sodium iodide and potassium iodide exposure were similar, except with slower onset and the absence of hemoglobinuria (Webster et al., 1957). Iodate salts have also been demonstrated to produce toxic retinopathy in animals and humans at doses of 40 mg/kg (IV) in rats and 187 mg/kg (oral) in humans (Singalavanija et al., 2000).

Data from repeated dose studies are limited. In an 8-week feeding study in rats, mortality was observed at 20,000 ppm PCOP. These animals also exhibited reduced hemoglobin and hematocrit values, severe body weight depression, lethargy and muscle weakness, pale/small spleens, and distended intestines containing pink mucous. Thyroid weight was increased in females in the 2,000 ppm PCOP group; thyroid weight was not evaluated in the 20,000 ppm group (Kuhajek and Andelfinger, 1970). In a 16-week study in which potassium iodate was administered to mice via drinking water, hemolysis and associated renal damage were observed at doses of 0.25% KIO₃ (approximately 540 mg/kg-day) and above (up to 1231 mg/kg-day), but no other adverse effects were observed (Webster et al., 1959). In a similar four-week study with guinea pigs, no effects were observed at doses up to 0.50% KIO₃ (approximately 485 mg/kg-day; LD₅₀ in guinea pigs <400 mg/kg) (Webster et al., 1959). The authors concluded that these results demonstrated that the toxicity of iodate is reduced when consumed in divided doses over time, when given with food (Webster et al., 1959). The lowered toxicity may be attributable to small doses of iodate being reduced to the less toxic iodide when in contact with food in the gastrointestinal tract.

The toxicity of periodate to the thyroid is of particular importance. Iodine is essential for normal thyroid function. Iodide is taken up by thyroid follicular cells, transported into the lumen, oxidized to iodine and used to make thyroid hormones (T₃ and T₄). Alteration of blood iodine levels can have profound effects on thyroid status. Dietary supplementation with iodized salt has long been practiced as a preventative measure and treatment for iodine-deficient goiter. Excess dietary iodide can also result in thyroid hyperplasia and goiter. High blood iodide levels disrupt thyroxinogenesis by blocking the release of T₃ and T₄ from the follicle (Capen and Martin, 1989). Iodate and iodide have been shown to be equally available to the thyroids of rats, rabbits, and humans (Burgi et al., 2001; Murray, 1953). Therefore, the increase in available iodine with periodate dosing may result in iodine-induced thyrotoxicosis.

To determine whether sodium periodate and/or potassium periodate provide reduced health hazard alternatives to currently fielded oxidizers, acute and subacute oral toxicity tests were conducted in rats.

The following table identifies the dates of critical study events.

Table 1. Critical Study Events

Critical Event	Date of Event
Animal Use Protocol Approved	06/26/2013
Study Initiation Date	06/27/2013
Acute Study Initiation	07/16/2013
Acute Study Necropsy	07/16/2013 – 08/14/2013
14-day Study Initiation	08/12/2013
14-day Study Scheduled Necropsy	08/26/2013 – 08/30/2013
Experimental Completion	11/03/2013
Study Completion	11/12/2014

5 Materials and Methods

5.1 Test Substance

Neat potassium periodate (CAS # 7790-21-8; lot 10174755; purity: 100.5%) and sodium periodate (CAS # 7790-28-5; lot B27Z025; purity: 99.07%) were purchased from Alfa Aesar, Ward Hill, MA. Dosing solutions/suspensions were prepared by weighing the required amount of potassium or sodium periodate and adding a measured volume of deionized water. For the acute study, fresh dosing solutions/suspensions were prepared for each day/round of dosing. For the 14-day study, six dosing solutions, 3.125, 6.25, 12.5, 25, 50, and 100 milligrams per milliliter (mg/ml) of sodium periodate, were prepared at the start of the study in sufficient volume for use throughout the study. A one milliliter sample was taken from each dosing solution and analyzed by Army Institute of Public Health (AIPH) Laboratory Sciences Portfolio via high performance liquid chromatography with ultra violet detection to verify the concentration. In addition, samples were collected from a representative solution (25 mg/ml) at approximately weekly intervals prior to the study to determine the stability of the dosing solutions. Results from the stability test indicated that the test compound was stable for at least five weeks when stored at room temperature. The dosing solutions were mixed on a stir plate for approximately ten minutes prior to taking analytical samples, prior to dosing, and continued to be mixed throughout the dosing procedure.

5.2 Animals*

This study was conducted using male and female Sprague Dawley (CrI:CD(SD) CD[®]) rats obtained from Charles River Laboratories, Wilmington, Massachusetts. All animals were housed in temperature-, relative humidity-, and light-controlled rooms. The target conditions of the rooms were 68-72 °F and 30-70 percent humidity. An automatically controlled 12:12-hour light/dark cycle

* Animal use procedures were approved by the United States Army Public Health Command (USAPHC) Institutional Animal Care and Use Committee. Animal care and use was conducted in accordance with *The Guide for the Care and Use of Laboratory Animals* and all applicable Federal and DOD regulations. The USAPHC Animal Care and Use Program is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

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was maintained, with the dark period beginning at 1800 hours. The mean temperature was 71 °F and ranged from 68 to 76 °F. The mean relative humidity was 54% and ranged from 49 to 92%. Relative humidity and temperature were out of range (73-92% and 73-76 °F) on 31 July 2014 from approximately 1030 until 1245. Room temperature was additionally out of range on 3 August from approximately 1015 to 1100 (73 °F). A certified pesticide-free rodent chow (Harlan Teklad®, 2016C Certified Rodent Diet) was available *ad libitum*. Filtered tap water was provided *ad libitum* via an automated watering system. Acute study rats were individually housed. Rats in the 14-day study were housed same sex pair housed by dosage group. All rats were housed in suspended polycarbonate cages with Diamond Dry® bedding. Each rat was uniquely identified by number via cage card and tail marking. (CD® is a registered trademark of Charles River Laboratories International, Inc.; Teklad® and Diamond Dry® are registered trademarks of Harlan, Teklad).

5.3 Contract Studies

Tissues were preserved, packaged, and shipped to Battelle, Columbus, OH, for processing, slide preparation, staining, and histopathologic evaluation. Tissues and slides were returned to the USAPHC for archiving. Data from the anatomic pathology report prepared by Battelle are discussed herein. The complete report can be found in Appendix N.

5.4 Quality Assurance

The AIPH Quality Systems Office audited critical study phases. Appendix B provides the dates of these audits, the phases audited and the dates that the results of the inspections were reported to the Study Director (SD) and Management.

5.5 Study Personnel

Appendix C lists the names of individuals contributing to the study performance.

5.6 Acute Study

The acute toxicity of sodium periodate and potassium periodate was assessed using the Sequential Stage-Wise Probit (SSWP) method (ASTM, 2010; Feder et al., 1991a; Feder et al., 1991b). This method proceeds in rounds in which groups of rats are dosed and the responses observed and used in determining the doses and number of animal used in the next round of dosing. In the first round, approximately five different doses of each of the test compounds were selected such that the doses spanned the entire dose response curve. In the absence of historical data or literature values, doses for the first stage of dosing were set at the default starting value of 175 mg/kg with half-log dose intervals (3.2 dose progression factor) (USEPA, 2002). One to two animals were given each dose in the first round of the acute study. In all subsequent rounds of dosing, one to four doses were used, with one to three animals at each dose. Animals were randomly assigned to doses. Dosing of rounds was separated by a post-dosing observation period of up to 14-days in which animals were observed for signs of toxicity, moribundity, and mortality. This period was reduced to 24-48 hours for determination of dosages in subsequent rounds when the survival of the animals could be confidently predicted. A probit analysis of the results from all previous rounds of dosing was used to determine the doses for subsequent rounds of dosing. The analysis uses the results from each stage to calculate the LD₅₀, 95% confidence interval, and slope of the dose response curve. Dosing of stages was continued until the variation around the LD₅₀ was less than 0.40 (95% upper confidence limit minus 95% lower confidence limit/2x the LD₅₀) or a maximum of 30 rats per sex were utilized.

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The Approximate Lethal Dose (ALD) method was also used to determine the acute toxicity of sodium periodate in fed female rats (Deichman and LeBlanc, 1943). This test was conducted to determine if differences exist between fasted (overnight) and fed lethal doses and to assist in determining dose levels for the 14-day study. The ALD test was conducted using the periodate salt to be tested in the 14-day study; the more toxic of the two periodate salts, sodium periodate. The ALD consisted of six doses and a control, with one female rat receiving each dose. Dose selection for the sodium periodate ALD was based on the results of the SSWP but included a 2-fold difference in LD₅₀s between fasted and fed animals that has been demonstrated for iodate (Webster et al., 1959). Dose intervals were set at approximately 1.5X the previous dose to a maximum of 2000 mg/kg. All animals were dosed on the same day. The ALD was defined as the lowest dose which was lethal where two successively higher doses were lethal and three lower doses were not lethal.

Fifty-eight female and forty-seven male Sprague Dawley (CrI:CD(SD) CD[®]) rats were used for the acute portion of this study. Females were approximately 10 weeks old and weighed 221.1 ± 15.3 grams (g), while males were approximately 9 weeks old and weighed 307.5 ± 19.0 g. All sodium periodate and potassium periodate doses were administered according to body mass measured on the day of dosing. Constant concentration dosing was used within each round of dosing. However, due to difficulties encountered in delivering the very concentrated suspensions without injuring the animals, the concentrations were reduced for subsequent rounds. Oral dosing was performed using a stainless steel 16 gauge x 2 inch gavage needle. All animals were observed for a period of 14 days during which clinical observations and body mass were measured daily during the week. Following the observation period, all animals were euthanized with CO₂ and submitted for gross pathological examination.

5.7 14-Day Oral Repeated Dose Toxicity Study

Upon evaluating the results of the SSWP and ALD, a 14-day oral toxicity study was performed to determine the effects of repeated daily dosing with sodium periodate.

5.7.1 Dose Selection and Test Substance Administration

For the 14-day study, sixty female (215.4 ± 11.1 g) and sixty male (269.8 ± 11.7 g) Sprague Dawley (CrI:CD(SD) CD[®]) rats approximately 10 weeks old were used. Assignment to dose groups was accomplished using a stratified random procedure, with animals stratified according to body mass and dose groups assigned randomly. Body mass did not differ among dose groups prior to initiation of dosing. Females and males were each divided into five time-separated necropsy groups, with animals from each test group approximately evenly distributed across necropsy groups.

Dose selection for the 14-day study was based on the results of the acute study (e.g., 0.5x, 0.25x, 0.125x, 0.0625x, 0.03125x the LD₅₀) with an adjustment factor for differences between fed and fasted rats calculated based on the results of the ALD. The vehicle control group received a volume equivalent to the highest exposure group.

All sodium periodate doses and the control were administered based on body mass and volume of solution at rates of 6.36 and 7.41 milliliter per kilogram (ml/kg) for females and males, respectively. Dosages were adjusted daily for changes in body mass. The sodium periodate solution and water control were administered between 0715 and 1000 daily. Oral dosing was performed using a stainless steel 16 gauge x 2 inch gavage needle.

5.7.2 Observations, Body Mass, Food Consumption

During the dosing period, observations for mortality and signs of toxic effects were made at least twice daily, once in the morning and once in the afternoon, except on weekends when observations occurred only in the morning. Additionally, each animal was removed from its cage daily for a clinical examination. Examinations included evaluation of skin and fur, eyes and mucous membranes. Respiratory and circulatory effects, autonomic effects such as salivation, central nervous system effects, including tremors and convulsions, changes in the level of activity, gait and posture, reactivity to handling or sensory stimuli, altered strength, and stereotypes or bizarre behavior (e.g., self-mutilation and walking backwards) were recorded.

Animals were weighed twice pre-study and on study days 0, 1, 3, 7, and 13. Terminal (fasted) body mass was obtained the morning of necropsy following overnight fasting. Feed was provided *ad libitum* seven days per week in weighed feeder bins. Feeders were reweighed study days 0, 1, 3, 7, and 13 and the mass of the empty feeder was subtracted from the mass of the full feeder to determine the grams of food consumed for each pair of animals. Because rats were pair housed and individual food consumption could not be determined, food consumption was then calculated on a per gram of rat by dividing the food consumed by the total mass of the rats in each cage. Food conversion efficiency was calculated as a ratio of food consumed to body mass gained.

5.7.3 Urinalysis

During the night prior to scheduled necropsy, each surviving animal was placed in a metabolism cage capable of separating urine and feces for a period of approximately 12 hours during which free-catch urine was collected. Animals were fasted during this period to coincide with fasting prior to necropsy. Water was available *ad libitum* via a water bottle containing a measured volume of water. Urine samples were transferred to clear, graduated conical centrifuge tubes and the volume, color, and appearance of each sample were recorded. The color of each sample was determined based on comparison with a urine color chart with nine colors ranging from pale yellow/straw to dark amber. Specific gravity was tested using a refractometer. Chek-Stix™ Test Strips were used to conduct chemical analyses including pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrites, and leukocytes. Water consumption was determined by pouring all water from spill containers back into the water bottle, reading the current empty volume, and subtracting that volume from the initial full volume. Chek-Stix™ is a registered trademark of Siemens Healthcare Diagnostics (Tarrytown, NY).

5.7.4 Necropsy

After 14-days of treatment, or when determined to be moribund, all surviving rats were anesthetized with CO₂, blood was collected by intracardiac puncture, and rats were euthanized using CO₂. Necropsies were scheduled over five days based on the staggered experimental start dates. Necropsy order was randomized across treatment groups. Rats that died during the course of the study were submitted for gross necropsy if the animal was determined to have died recently. Tissues that were not grossly autolytic were submitted for histopathologic evaluation.

A full, detailed gross necropsy including a careful examination of the external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities and their contents was performed on all experimental animals following euthanasia. At necropsy, the adrenals, brain, heart, kidneys, epididymides, liver, ovaries (without oviducts), spleen, testes, thymus, thyroid (with attached portion of trachea), and uterus were removed, trimmed, and weighed (except the thyroid/trachea, which

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was preserved prior to weighing). Kidneys, adrenals, and ovaries were weighed as pairs. Any observed lesions were retained for processing. In addition to the organs listed above, samples of peripheral nerve, muscle, spinal cord, eye plus optic nerve, gastrointestinal tract, urinary bladder, lung, bone marrow, pituitary, and vagina were collected and placed in 10% buffered formalin.

The adrenals, brain, heart, kidneys, liver, ovaries (without oviducts), spleen, thymus, thyroid (with attached portion of trachea), and uterus were placed in 10% buffered formalin for at least 24 hours for fixation. The thyroid (with parathyroids) was then dissected from the trachea, blotted and weighed to the nearest 0.01 mg. The testes and epididymides from each animal were placed in Davidson's fixative overnight (no longer than 24 hours). After fixation, all tissues were rinsed and stored in 70% ethanol.

5.7.5 Histopathology

After tissues were fixed, specified tissues were packaged and shipped to Battelle, Columbus, OH for processing and histopathologic examination. Tissues were selectively trimmed and slides prepared and submitted for histologic examination. All processed and embedded tissues were microtomed at 5 micrometers (μm) thick and stained with hematoxylin and eosin.

Slides were examined by a board-certified veterinary pathologist, with diagnoses entered into the Xybio Next Generation data-management system under "blind" mode. Specimens were processed and initially examined microscopically in "blinded" fashion (without knowledge of dose group). Once the slides were examined, the raw blinded data were submitted to the Study Director for review, and the case numbers were "un-blinded" (identified as to treatment or control group). The pathologist examined slides for compound-induced histopathologic changes via light microscopy. Sections of adrenal glands, brain, epididymides, heart, intestine (large and small), kidneys, liver, ovaries, spleen, stomach, testes, thymus, thyroid, and uterus (as appropriate) were trimmed, slides prepared, and these were submitted for histologic examination. In addition, selected tissues with gross observations saved at necropsy were also trimmed, processed, and accompanied the slide set for examination.

A variety of non-neoplastic lesions were noted in various tissues, and were semi-quantitatively graded across a 4-point scale, where Grade 1 (minimal) referred to a minor change of negligible biologic significance or which affected less than 10 percent of the presented tissue area, and Grade 2 (mild) referred to a greater change which affected 10 to 19 percent of the tissue area. Grade 3 (moderate) was scaled to refer to a change of clear biologic relevance and which affected at least 20 percent of the tissue area, and Grade 4 (marked) was scaled for lesions considered to be of maximal morphologic change. For the thyroid gland, an additional microscopic notation was made for all rats. Thyroid follicular epithelium was evaluated for increased size (hypertrophy and height) and graded on a 1 to 5 scale. Follicular epithelium that was predominately flattened was graded as 1; whereas follicular epithelium that was all tall columnar in morphology was graded as 5. Mostly cuboidal-shaped epithelium constituted a grade of 3. Grades 2 or 4 were used for variations between these appearances.

5.7.6 Clinical Chemistry and Hematology

Blood for clinical chemistry analyses was transferred to collection tubes free of additives and was allowed to clot at room temperature for 30 to 40 minutes, was centrifuged for approximately 2.5 minutes at 12,000 x g. Serum was removed and immediately analyzed for clinical chemistry parameters. Aliquots (100 microliters (μl)) were also placed in siliconized tubes and stored at

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approximately -35 °C for subsequent thyroid hormone assays (triiodothyronine (T₃), total thyroxine (T₄), (TSH)). The following clinical chemistry parameters were evaluated using the Idexx VetTest[®] 8008 Chemistry Analyzer and the VetLyte[®] Electrolyte Analyzer: albumin (ALB), alkaline phosphatase (ALKP), alanine aminotransferase (ALT), amylase (AMYL), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium (CA), cholesterol (CHOL), creatinine (CREA), globulin (GLOB), glucose (GLU), total bilirubin (TBIL), total protein (TP), sodium (Na), phosphate (PHOS), potassium (K), and chloride (Cl). (VetTest[®] and VetLyte[®] are registered trademarks of IDEXX Laboratories, Inc.).

Blood for hematology analyses was transferred to tubes containing tripotassium ethylenediamine-tetraacetic acid (K₃EDTA). The following hematology parameters were evaluated using the Cell-Dyn 3700 Hematology Analyzer (Abbott Laboratories, Abbott Park, IL 60064): erythrocyte count (RBC), hematocrit (HCT), hemoglobin concentration (HGB), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red blood cell distribution width (RDW), total white blood cell count (WBC), and differential leukocyte count (neutrophils: NEU, lymphocytes: LYM, monocytes: MONO, eosinophils: EOS, basophils: BASO), platelet count (PLT), and mean platelet volume (MPV). To determine average activated prothrombin time, blood was transferred to a tube containing sodium citrate, the blood mixed, then centrifuged for approximately 2.5 minutes at 12,000 x g. The plasma was analyzed using the MCA 210 Microsample Coagulation Analyzer (BioData Corporation, Horsham, PA 19044).

5.7.7 Thyroid Hormone Assays

Triiodothyronine and total thyroxine were determined using the TOSOH[®] Bioscience AIA[®]-360 Automated Enzyme Immunoassay System. TOSOH[®] and AIA[®] are registered trademarks of Tosoh Corporation.

Analysis of TSH was conducted using a commercially available rat TSH Enzyme linked Immunosorbant Assay kit purchased from ALPCO[™] Immunoassays. Due to detection of interfering substances during assay validation, samples were pre-treated by precipitation with 25% polyethylene glycol (PEG-6000) prior to use in the assay (Dimeski, 2008; Sakai et al., 2009; Tate and Ward, 2004). PEG-6000 (100 µl) was added to each sample, the sample was vortexed and then centrifuged for approximately 5 minutes at 4000 x g. Assays were then conducted using the supernatant according to the manufacturer's instructions as follows. Assay materials were equilibrated to room temperature prior to use in the assay. Twenty-five microliters (µl) of standard (Lot 001), blank (Lot 007), or sample was added, in duplicate, to the appropriate wells of the 96-well plate (Lot 012) pre-coated with TSH monoclonal antibodies. Enzyme-labeled anti-rat TSH-antibody (200 µl) (Lot 008) was then added to all wells, the plate covered with the adhesive strip, and the plate incubated for 18-20 hours at 4±2 °C. The plate contents were discarded and the plate was washed four times with 300 µl of diluted wash solution (Lot 044). Tetra-Methyl-Benzidine substrate solution (Lot 019) (200 µl) was added to each well and the plate incubated in the dark for 30±1 minutes at room temperature (approximately 19 °C). Stop solution (Lot 019) (50 µl) was added to each well, the plate gently mixed to ensure completion of color change, and the plate read within 15 minutes. The optical density of each well was determined at 450 nanometers (nm) and 630 nm using a BioTek[®] Synergy HT Multi-Mode microplate reader with Gen5[™] data analysis software. Mean absorbance for each sample was calculated after adjustment for the absorbance at 630 nm. The TSH values were calculated from the calibration curve for each assay using ReaderFit[®] software. The external quality control standards (Rat Control 1 and 2 Lot 001) were within the target reference ranges. The intra-assay coefficients of variation were 2.6% and 1.8%, respectively, and the inter-assay coefficients of variation were 6.7% and 8.8%, respectively.

ALPCO™ is a registered trademark of ALPCO Diagnostics, BioTek® and Gen5™ are registered trademarks of BioTek Instruments, Inc., and ReaderFit is copyrighted by Hitachi Solutions America, Ltd.

5.8 Data Collection and Statistical Analyses

Experimental data generated during the course of this study were recorded by hand and tabulated, summarized, and/or statistically analyzed using Microsoft® Excel, SAS®, and SPSS® 21.0. Environmental data were automatically recorded using MetaSys® Building Management System. Microsoft® is a registered trademark of Microsoft® Corporation, SAS® is a registered trademark of SAS Institute Inc., SPSS® is a registered trademark of IBM Corp., and MetaSys® is a registered trademark of Johnson Controls.

Data from the SSWP were analyzed according to the methods of Feder et al. (Feder et al., 1991a; Feder et al., 1991b) to determine the LD₅₀, 95% confidence interval, and slope of the dose response curve. The ALD was determined as the lowest dose which was lethal where two successively higher doses were lethal and three lower doses were not lethal. The ALD was then compared to the LD₅₀ from the SSWP to estimate an adjustment factor between fasted and fed rats for use in determining doses for the subacute study.

Data from the subacute study were analyzed based on the type of data collected and the frequency of collection. Variables measured only at the end of the study were analyzed using a one-factor Analysis of Variance (ANOVA) with dose group as the main effect. Organ to brain and organ to body mass ratios were calculated and analyzed similarly to the other parameters measured at the end of the study. Absolute organ mass was analyzed by Analysis of Covariance (ANCOVA), with dose group as the main effect and body mass at the end of the study as the covariate (Bailey et al., 2004). Interpretation of changes in absolute organ mass, organ-to-body mass ratio, and organ-to-brain mass ratio in the evaluation of compound related effects was based on published analysis of control animal data (i.e., organ-to-body mass ratio: liver and thyroid; organ-to-brain mass ratio: adrenals ovaries; ANCOVA: brain, heart, kidney, testes) (Bailey et al., 2004). Parameters measured multiple times during the study (i.e., body mass, food consumption) were analyzed using repeated measures ANOVA with sample day as the within subject factor and dose group as the between subject factor. If the interaction between within and between subject factors was significant, the effect of dose group on the parameter was determined within each sampling day using a one-factor ANOVA. Ordinal urinalysis data were coded for analysis by ANOVA. When significant main effects were observed ($p < 0.05$), appropriate post hoc tests were used to compare dose groups to the control group [e.g., Tukey's multiple comparison test, Dunnett's T3 (if variances are unequal), or Sidak (for ANCOVA)]. Data were evaluated for homogeneity of variance by Levene's test. The following hematology, clinical chemistry, and hormone parameters violated the assumptions of normality and were analyzed using nonparametric tests (Mann-Whitney U): T3, TSH, NEU, %NEU, %LYM, MONO, %MONO, EOS, HGB, HCT, MCHC, RDW, ALT, AMYL, BUN, CREA, GLOB, TBIL, Na, Cl, PLT, Ca.

6 Results

6.1 Analytical Chemistry

The analytical chemistry results are summarized in Table 2. All results were within the 70-130% recovery limits for the analysis. As such, all results were reported using the nominal concentrations. Stability analyses indicated that storage time and conditions were acceptable.

Table 2. Sodium Periodate Analytical Results

Sodium Periodate Sample Type	Date	Nominal Concentration (mg/ml)	Analytical Concentration (mg/ml)	% of Nominal	% of Initial
Stability Test 1	8/2/2013	25	24	96	
Stability Test 2	8/7/2013	25	24		96
Stability Test 3	8/13/2013	25	27		108
Stability Test 4	8/20/2013	25	25		100
Stability Test 5	8/27/2013	25	26		104
Concentration verification	8/13/2013	3.1	3.4	109	
Concentration verification	8/13/2013	6.3	6.5	104	
Concentration verification	8/13/2013	12.5	12	96	
Concentration verification	8/13/2013	25	26	104	
Concentration verification	8/13/2013	50	51	102	
Concentration verification	8/13/2013	100	100	100	
Concentration verification	8/27/2013	3.1	3.3	106	

6.2 Acute Study

6.2.1 Sequential Stage-Wise Probit (SSWP)

6.2.1.1 Potassium Periodate

Clinical signs including lethargy, rough coat, labored breathing, prostration, laying on side, squinting, dark eyes, hunched posture, chromodacryorrhea, diarrhea, bloody urine, and red discharge from nose were noted in males and females given single oral doses of potassium periodate of 560 mg/kg and greater. Clinical signs occurred in females and males given doses of 560 mg/kg or greater and were typically apparent approximately fifteen to thirty minutes after dosing and persisted throughout the first day of observation in surviving animals. Mortality occurred in female rats at doses of 650 mg/kg and greater, occurring 1.5 to 6+ hours after dosing. Mortality occurred in male rats at doses of 560 mg/kg and greater, occurring 2.5 to 6+ hours after dosing (see Appendix D for details). Gross pathology observations included mottled kidneys with dark red medulla, fluid filled intestines, glandular stomach mucosa bright red, mottled liver, dark spleen, enlarged kidneys, pale medulla of kidneys, yellow fluid in throat, red urine in bladder, foamy white fluid in esophagus. The resulting LD₅₀ from the probit analysis for females was 732 mg/kg with a confidence interval of 539-838 and a slope of 13.4. For males, the LD₅₀ was 685 mg/kg with a confidence interval of 580-809 and a slope of 10.6.

6.2.1.2 Sodium Periodate

Clinical signs including lethargy, rough coat, labored breathing, prostration, squinting, dark eyes, hunched posture, chromodacryorrhea, diarrhea, bloody urine, and red discharge from nose were noted in males and females given single oral doses of sodium periodate. Clinical signs occurred in females and males given doses of 175 mg/kg or greater and were typically apparent approximately fifteen to thirty minutes after dosing and persisted throughout the first day of observation in surviving animals. Mortality occurred in female rats at doses of 290 mg/kg and greater, occurring

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50 minutes to over 6 hours after dosing. Mortality occurred in male rats at doses of 400 mg/kg and greater, occurring one hour to three days after dosing (see Appendix D for details). Gross pathology observations included dark red spleen, dark liver, vascular congestion in stomach and cecum, focal grey and focal red areas in stomach, glandular stomach mucosa red, thickened stomach lining, medulla of kidneys dark red, intestines distended with clear fluid, lungs grey and spongy, viscous material in non-glandular stomach, cortico-medullary junction of kidneys pale, liver pale and firm, contents of intestines orange/red, foamy white fluid in esophagus, focal pale and red areas with irregular edges on liver, and dilated vasculature of the heart and cecum. The resulting LD₅₀ from the probit analysis for females was 318 mg/kg with a confidence interval of 292-347 and a slope of 24.3. For males, the LD₅₀ was 741 mg/kg with a confidence interval of 704-779 and a slope of 31.2.

6.2.2 Approximate Lethal Dose (ALD)

Clinical signs including lethargy, rough coat, labored breathing, prostration, squinting, hunched posture, and blood stained bedding were noted in females given single oral doses of sodium periodate of 283 mg/kg and greater. Clinical signs were typically apparent approximately fifteen to thirty minutes after dosing and persisted throughout the first day of observation in surviving animals. The only mortality was the 1431 mg/kg animal (see Appendix D for details). As such these data do not conform to the prescribed framework for defining an ALD (i.e., there weren't three higher doses with mortalities). For the purposes of deriving a fasted versus fed adjustment factor, the ALD was defined as 1431 mg/kg in fed female rats.

6.3 14-Day Study

6.3.1 Clinical Observations and Mortality

Lethargy, squinting, congested breathing, prostration, hunched posture, rough coat, bloody bedding in cage, bloody urination, dried red material on front paws, brown perianal staining, diarrhea, bloody discharge from nose when dosed, and barbering were noted in female rats in the 318 mg/kg-day group and male rats in the 185, 370, and 741 mg/kg-day groups. Chromodacryorrhea was observed in one female rat in each of the 40 and 159 mg/kg-day sodium periodate groups. Two additional females in the 40 mg/kg-day group had soft feces and bloody discharge from the nose during dosing. Five females in the 318 mg/kg-day sodium periodate group were terminated after approximately 8 days of dosing due to moribund condition. All others females survived to study termination. All males in the 370 and 741 mg/kg-day sodium periodate groups died or were terminated due to moribund condition after approximately 8 and 4 days, respectively. One male in the 185 mg/kg group was terminated due to moribund condition at day 13. See Appendix D for details.

6.3.2 Body Mass and Food Consumption

The initial mean body mass of the water control rats was 224.3 and 292.2 g for females and males, respectively. In female rats treated with sodium periodate, initial body mass ranged from 221.5 to 228.9 g and generally increased throughout the study for all dose groups. However, females in the 159 and 318 mg/kg-day groups experienced reduced, relative to the control, body mass gain between days 7-13 and overall ($p=0.001$ and $p<0.001$, respectively). Females in the 318 mg/kg-day group additionally had reduced body mass gain between days one and three ($p=0.002$), demonstrating a net loss during that time period. Body mass was reduced (11.7%), relative to the control group, in the 318 mg/kg-day group only at day 13 ($p=0.028$). In male rats treated with

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sodium periodate, initial body mass ranged from 281.5 to 290.7 g. Body mass increased over time for males in the 47, 93, and 185 mg/kg-day groups, but decreased for males in the 370 and 741 mg/kg-day groups. Males in the 370 mg/kg-day group had reduced body mass gain relative to the control group and a net loss of body mass at days 1-3 and 3-7 ($p<0.001$ and $p<0.001$, respectively). Males in the 741 mg/kg-day group lost weight and had reduced body mass gain relative to the control throughout their survival on study (days 0-1: $p=0.002$ and days 1-3: $p<0.001$). Body mass gain was also reduced in males in the 185 mg/kg-day at days 7-13 and overall ($p<0.001$ and $p<0.001$, respectively). Body mass was reduced by 14.4% at day 13 ($p=0.006$) in the 185 mg/kg-day group. In the 370 and 741 mg/kg-day groups, body mass was reduced by 8.8% and 15.6% at day 3 ($p<0.001$ and $p<0.001$, respectively) and by 19.3% at day 7 in the 370 mg/kg-day group ($p<0.001$). See Appendices E and F for details.

Food consumption and food conversion efficiency did not differ between treated and control groups for either males or females when measured at time points within the study (i.e., measured on days 1, 3, 7, and 13). Total or net consumption and food conversion measured across the entire study differed between treated and control groups for both females and males. Total food consumption was reduced, relative to the control, in females given 318 mg/kg-day sodium periodate ($p<0.001$). In males, total food consumption was reduced, relative to the control, in the 185, 370, and 741 mg/kg-day groups ($p=0.013$, $p<0.001$, $p<0.001$, respectively). See Appendix G for details. Net food conversion efficiency (i.e. 14-day) was reduced in female rats given 80, 159, and 318 mg/kg-day sodium periodate ($p=0.041$, $p<0.001$, $p<0.001$, respectively). In male rats, net food conversion efficiency (i.e. 14-day) was reduced in the 185 mg/kg-day group ($p=0.028$). See Appendix H for details.

6.3.3 Urinalysis

In females, urine volume was increased (2.5 fold) and urine specific gravity decreased in the 159 mg/kg-day sodium periodate dose group ($p=0.043$ and $p=0.012$, respectively). Water intake was generally increased in the 80, 159, and 318 mg/kg-day groups (1.3, 2.5, 1.9 fold, respectively); however, these increases were not significant. Urine pH was increased in females in the 80 and 159 mg/kg-day group compared to the control group ($p<0.001$ and $p<0.001$, respectively). In the 318 mg/kg-day group, increased amounts of blood were found in the urine ($p<0.001$). The remaining urine parameters: color, appearance, glucose, bilirubin, ketone, protein, urobilinogen, nitrites, and leucocytes did not differ between sodium periodate treated and control groups for females. In males, the measured urine parameters were unaffected by sodium periodate treatment in the dose groups that survived to the time of urinalysis. Water intake and urine volume were, however, slightly increased, relative to the control, in the 185 mg/kg-day group (2.2 and 1.5 fold, respectively) as was observed in females. Blood was also noted in the urine of several males in the 185 mg/kg-day group. See Appendix I for details.

6.3.4 Pathology

Red areas were noted in the stomachs of three of 10 females in the 318 mg/kg-day sodium periodate group. Additional gross pathology findings in individual females in the 318 mg/kg-day group included red mesenteric lymph nodes, pale liver, red outer rim of medulla of kidney, and fluid-filled cyst surrounding adrenal gland. Clear mucous in the cecum and/or yellow liquid in the gastrointestinal tract were noted in six of 10 females in the 318 mg/kg-day group. Yellow fluid was also noted in the gastrointestinal tract of females in the 40 (three of 10) and 80 (two of 10) mg/kg/day groups. Additional findings in females included hydrouterus (three control, four 20

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mg/kg-day, one 40 mg/kg-day, one 80 mg/kg-day, two 159 mg/kg-day, and two 318 mg/kg-day) and mottled liver (one control, one 20 mg/kg-day, two 40 mg/kg-day, and two 159 mg/kg-day).

Red areas were noted in the stomachs of four of nine males in the 370 mg/kg-day and three of eight males in the 741 mg/kg-day sodium periodate group. Raised white areas and cysts-like areas in the glandular stomach were also noted in one male rat in each of the 370 and 741 mg/kg-day groups. One male rat in the 185 mg/kg-day group was noted as having sloughing of the lining of the stomach. Red mesenteric lymph nodes were noted in three of nine males in the 370 mg/kg-day and five of eight males in the 741 mg/kg-day sodium periodate group. In males, the kidneys were noted as being pale (cortex) in five rats (two 40 mg/kg-day, one 80 mg/kg-day, and one 370 mg/kg-day) and were noted as being dark or dark red (medulla) in four rats (one 370 mg/kg-day and three 741 mg/kg-day). Yellow fluid was noted in the gastrointestinal tract of males in the 182.5 (five of 10), 370 (six of nine), and 741 (five of eight) mg/kg/day groups. Clear mucous in the cecum was also noted in five males (one 185 mg/kg-day and four 370 mg/kg-day group). Mottled and/or dark liver was noted in 23 males (six control, four 47 mg/kg-day, three 93 mg/kg-day, two 185 mg/kg-day, six 370 mg/kg-day, and two 741 mg/kg-day). Additional gross pathology findings included: blood on underside of brain (one 370 mg/kg-day and two 741 mg/kg-day), ulceration on tongue (one 741 mg/kg-day), pale/spongy lungs (one 370 mg/kg-day and one 741 mg/kg-day), pale salivary glands and thymus (one 370 mg/kg-day), and dark spleen (one control and one 47 mg/kg-day).

Bedding was found in the stomach and/or intestinal tract of 34 females (six controls, seven 20 mg/kg-day, eight 40 mg/kg-day, two 80 mg/kg-day, five 159 mg/kg-day, and six 318 mg/kg-day) and 24 males (five control, five 47 mg/kg-day, six 40 mg/kg-day, four 80 mg/kg-day, two 159 mg/kg-day, and two 714 mg/kg-day). No additional gross lesions were noted at the time of necropsy.

6.3.5 Organ Mass and Ratios

6.3.5.1 Females

Adrenal, heart, kidney, ovary, liver, spleen, and thymus mass and/or mass ratios differed between the 318 mg/kg-day sodium periodate group and the control. Mean absolute heart, kidney, ovary, spleen, and thymus mass were reduced (0.8, 0.9, 0.8, 0.7, and 0.6 fold, respectively) in the 318 mg/kg-day group relative to the control ($p=0.001$, $p=0.037$, $p=0.003$, $p=0.001$, and $p=0.040$, respectively). Spleen to body mass and spleen to brain mass ratios were also reduced in the 318 mg/kg-day group ($p=0.042$ and $p=0.004$, respectively). Heart and ovary to brain mass ratios were reduced in the 318 mg/kg-day group ($p=0.021$ and $p=0.005$, respectively). Adrenal and liver to body mass ratios were increased in the 318 mg/kg-day group ($p<0.001$ and $p<0.001$, respectively). Adrenal and liver mass were also increased in the 318 mg/kg-day group when analyzed using body mass as a covariate ($p=0.024$ and $p<0.001$, respectively). Liver mass was additionally, increased in the 80 and 159 mg/kg-day groups when analyzed using body mass as a covariate ($p=0.026$ and $p<0.001$, respectively). Brain, thyroid, and uterus mass were unaffected by sodium periodate treatment. See Appendix J for details.

6.3.5.2 Males

Adrenal, brain, epididymides, heart, kidney, liver, spleen, testes, and thymus mass and/or mass ratios differed between the 185, 370, and 741 mg/kg-day sodium periodate group and the control. Mean absolute spleen mass was reduced (0.8, 0.5, and 0.5 fold, respectively) in the 185, 370, and 741 mg/kg-day groups relative to the control ($p=0.045$, $p<0.001$, and $p<0.001$, respectively).

Spleen to body mass ratios and spleen to brain mass ratios were also reduced in the 370 (0.6 and 0.5 fold; $p<0.001$ and $p<0.001$, respectively) and 741 mg/kg-day groups (0.6 and 0.5 fold; $p=0.001$ and $p<0.001$, respectively). Mean absolute heart mass was reduced in the 185 and 370 mg/kg-day groups (0.7 and 0.8 fold; $p=0.001$ and $p=0.004$, respectively). Heart to brain mass ratio was also reduced in the 185 mg/kg/day group (0.8 fold; $p=0.008$); however, heart to body mass ratio was increased in the 741 mg/kg-day group (1.2 fold; $p=0.011$). Mean absolute mass of the epididymides was reduced in the 370 and 741 mg/kg-day groups (0.7 and 0.6 fold; $p<0.001$ and $p<0.001$, respectively). Epididymides to brain mass ratio and epididymides mass analyzed using body mass as a covariate were also reduced in the 370 (0.8 and 0.8 fold; $p=0.001$ and $p=0.012$, respectively) and 741 mg/kg-day groups (0.7 and 0.6 fold; $p<0.001$ and $p=0.002$, respectively). Mean absolute brain mass was decreased in the 741 mg/kg-day group (0.9 fold; $p=0.021$); however, brain to body mass ratios were increased in the 370 and 741 mg/kg-day groups (1.2 and 1.3 fold; $p<0.001$ and $p<0.001$, respectively). Mean absolute liver mass was decreased in the 741 mg/kg-day group (0.8 fold; $p=0.045$). Adrenal to body mass ratios were increased in the 370 mg/kg-day group (1.5 fold; $p=0.001$). Testes to body mass ratios were increased in the 370 and 741 mg/kg-day groups (1.3 and 1.3 fold; $p<0.001$ and $p<0.001$, respectively). Mean absolute thymus mass (0.6, 0.4, and 0.4; $p=0.001$, $p<0.001$, and $p<0.001$, respectively), thymus to body mass ratios (0.7, 0.5, and 0.5 fold; $p=0.009$, $p<0.001$, and $p<0.001$, respectively), and thymus to brain mass ratios (0.6, 0.4, 0.4 fold; $p=0.001$, $p<0.001$, and $p<0.001$, respectively) were decreased in the 185, 370, and 741 mg/kg-day groups. Thyroid mass was unaffected by sodium periodate treatment. See Appendix J for details.

6.3.6 Histopathology

6.3.6.1 Females

Treatment-related changes were observed in the thymus, spleen, kidneys, stomach, mesenteric lymph nodes, liver, and intestine sections in female rats. Treatment-related changes in the thymus consisted of loss of cortical and/or medullary lymphocytes. Atrophy of the thymus was noted in all groups, including the control group (two of 10 rats; severity 1), the incidence and severity were greater in the 318 mg/kg-day group (nine of 10 rats; severity 2.2). The minimal thymic atrophy in the control group was interpreted to be consistent with aging and involution.

A similar change was observed in the spleen which manifested itself as loss of lymphocytes in splenic nodules and was coded as white pulp atrophy. White pulp atrophy was noted in one of 10 females in the 40 mg/kg-day group and six of 10 females in the 318 mg/kg-day group and was not noted in other groups. Also in the spleen, loss of extramedullary hematopoietic elements (red and white cell precursors) and contracted sinuses or red pulp atrophy was noted in four of 10 females in the 318 mg/kg-day group. Red pulp atrophy was not noted in other dose groups. These histologic changes correlated with gross notations of small thymus or spleen.

In the kidneys, acute tubular necrosis was noted in three of 10 females in the 318 mg/kg-day group (severity 1.7). Accumulation of eosinophilic hyaline droplets within renal tubular epithelium was also noted in females in the 318 mg/kg-day group (two of 10 rats; severity 1.5). Mineralization of necrotic cells was also noted in sodium periodate treated females (four, three, one, two, and zero rats in the 20, 40, 80, 159, and 318 mg/kg-day groups, respectively). Scattered foci of mineralization, which is occasionally seen in untreated rats, were present in one control. These changes corresponded to gross notations of kidney discoloration (red/brown/pale).

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In the stomach, treatment-related changes in the 318 mg/kg-day group consisted of mucosal (epithelial cell) ulcer/erosion in the forestomach (one of 10 rats; severity 1), areas of necrosis in the glandular stomach (two of ten rats; severity 1), hemorrhage (two of 10 rats; severity 2) and inflammation (two of ten rats; severity 1). These changes corresponded to gross notations of the stomach – blood, cyst, nodule, or raised area.

In the 318 mg/kg-day group, mesenteric lymph nodes were noted to be red on gross examination in one female. Microscopically, these were confirmed as nodes with sinus hemorrhage with sinus infiltration of histiocytes. These findings were attributed to treatment with periodate.

In the liver, necrosis was noted in one of 10 females in the 318 mg/kg-day group (severity 1). This finding was attributed to periodate administration. The gross notation of mottled liver had no microscopic correlate and was presumably due to hepatic sinusoid congestion.

The large intestinal sections in the 318 mg/kg-day group had areas of inflammation (one of 10 rats; severity 1) and mononuclear cell infiltrate (one of 10 rats; severity 2). These were attributed to toxic effects on the intestinal tract.

In females, mean follicle height score was 1.8, 2.0, 1.8, 1.7, 1.7, and 1.4 in control, 20, 40, 80, 159, and 318 mg/kg-day groups, respectively. Follicle score did not differ between treated and control groups. A follicle score of one is defined as normal in the scoring scheme (USEPA, 2009a, b).

Other incidental changes noted in organs examined were interpreted to be background or not of biologic or toxicologic relevance. See Appendix N details.

6.3.6.2 Males

Treatment-related changes were observed in the thymus, spleen, kidneys, stomach, mesenteric lymph nodes, liver, intestines, and the epididymides and testes of males. As with females, treatment-related changes in the thymus consisted of loss of cortical and/or medullary lymphocytes, or increased thymocyte apoptosis. Atrophy of the thymus was noted in all groups, including the control group (two of 10 rats; severity 1), the incidence and severity were greater in the 185, 370, and 741 mg/kg-day groups (five of 10, nine of nine, and eight of eight rats; severity 1, 2.8, and 3.1, respectively). The minimal thymic atrophy in the control group was interpreted to be consistent with aging and involution.

In the spleen, loss of lymphocytes in splenic nodules or white pulp atrophy was noted in the 185, 370, and 741 mg/kg-day groups and increased in frequency and severity with dose (three of 10, eight of nine, and eight of eight rats; severity 1.7, 2, and 2.5, respectively). Red pulp atrophy was noted in the spleens of males in the 185, 370, and 741 mg/kg-day groups (one of ten, eight of nine, eight of eight rats; severity 3, 1.5, 2, respectively). Red pulp atrophy was not noted in other dose groups.

In the kidneys, acute tubular necrosis was noted in the 185, 370, and 741 mg/kg-day groups (one of 10, seven of nine, and six of eight rats; severity 3, 2, and 1.5, respectively). Accumulation of eosinophilic hyaline droplets within renal tubular epithelium was also noted in males in the 741 mg/kg-day group (two of eight rats; severity 2). Mineralization of necrotic cells was also noted in the 185, 370, and 741 mg/kg-day groups (one of 10, three of nine, and three of eight rats; severity 1, 1.7, and 1, respectively).

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In the stomach, treatment-related changes in the 185, 370, and 741 mg/kg-day groups consisted of mucosal (epithelial cell) ulcer/erosion in the forestomach (one of 10, two of nine, and two of eight rats; severity 2, 2.5, and 3, respectively), areas of necrosis in the glandular stomach (one of ten, four of nine, and five of eight rats; severity 1, 1, 1, respectively), hemorrhage (zero of 10, three of nine, and two of eight rats; severity 0, 2, and 4, respectively) and inflammation (one of ten, four of nine, and three of eight rats; severity 3, 1.8, and 1.7, respectively).

In males, mesenteric lymph nodes were noted to be red during gross examination in four of nine rats in the 370 mg/kg-day group and six of eight rats in the 741 mg/kg-day group. Microscopically, these were confirmed as nodes with sinus hemorrhage (four of four and six of six rats; severity 3.5 and 3.5, respectively) with rare lymphocyte atrophy (two of four and four of six rats; severity 2 and 1.3, respectively). These findings were attributed to treatment with sodium periodate.

In the liver, necrosis was noted in one of eight males in the 741 mg/kg-day group (severity 1). This finding was attributed to sodium periodate administration.

The large intestinal sections from males in the 185 and 741 mg/kg-day sodium periodate groups had areas of inflammation (one of 10 and one of eight rats; severity 1 and 1, respectively), and hemorrhage (one of eight in the 741 mg/kg-day group; severity 1), or mononuclear cell infiltrate (one of 10 in the 185 mg/kg-day group; severity 2). In the small intestine, inflammation was noted in one of 10 males in the 185 mg/kg-day group (severity 2). These findings were attributed to toxic effects on the intestinal tract.

Males in the 185, 370, and 741 mg/kg-day groups had minimal to mild alterations of their testes (four of 10, nine of nine, and six of eight rats; severity 1.3, 1.3, and 1). Morphologically, this consisted of seminiferous tubules containing fewer germinal epithelial cells, often leaving a larger and empty tubular lumen with fewer mature spermatozoa. A similar morphologic appearance was noted in one control male and two males in the 47 mg/kg-day group (severity 1 and 1, respectively), so it was interpreted that increased incidence and severity, when compared to the controls, were the hallmarks of this treatment-related change. Hypospermia in the epididymides was also noted for one of 10 males in the 185 mg/kg-day group (severity 3). Epididymal granulomas were noted in one male in each of the 185 and 741 mg/kg-day groups (severity 4 and 2, respectively).

In males, mean follicle height score was 2.4, 2.2, 2.4, 2.0, 1.9, and 1.8 in control, 47, 93, 185, 370, and 741 mg/kg-day groups, respectively. Follicle score did not differ between treated and control groups. A follicle score of one is defined as normal in the scoring scheme (USEPA, 2009a, b).

Other incidental changes noted in organs examined were interpreted to be background or not of biologic or toxicologic relevance. See Appendix N for details.

6.3.7 Clinical Chemistry

6.3.7.1 Females

Cholesterol levels increased in a dose dependent manner in sodium periodate treated females, were higher (1.2, 1.4, 1.5 and 1.6 fold, respectively) in the 40, 80, 159, and 318 mg/kg-day groups than in the control group ($p=0.017$, $p=0.003$, $p=0.001$, and $p<0.001$), and were outside of normal ranges. Alkaline phosphatase (ALKP) levels were reduced in the 80, 159, and 318 mg/kg-day sodium periodate groups (0.8, 0.8, and 0.6 fold, respectively) relative to the control group ($p=0.037$, $p=0.045$, and $p=0.002$, respectively). The ALKP values for sodium periodate treated females were,

however, within reported normal values while that of the control was slightly above reported normal levels. All ALKP values were within historical normal ranges for the performing laboratory. Alanine aminotransferase (ALT) and amylase (AMYL) were elevated in the 318 mg/kg-day group (1.3 and 1.8 fold; $p=0.005$ and $p=0.014$, respectively) and were above reported normal values. Serum chloride levels were slightly decreased in females in the 318 mg/kg-day group ($p=0.008$) relative to the control group and were slightly decreased compared to published normal ranges.

6.3.7.2 Males

Cholesterol levels increased in a dose dependent manner in males in all sodium periodate treatment groups, were higher (1.3, 1.4, 1.6, 2.0 and 2.2 fold, respectively) in the 47, 93, 185, 370, and 741 mg/kg-day groups than in the control group ($p=0.037$, $p=0.006$, $p=0.001$, $p=0.013$, and $p=0.002$), and were outside of normal ranges. Alkaline phosphatase (ALKP) levels were reduced, relative to the control group, in the 182.5 mg/kg-day sodium periodate group (0.7 fold; $p=0.008$), but were increased in the 741 mg/kg-day group (1.4 fold; $p=0.032$). The ALKP values for both sodium periodate treated and control groups were above normal ranges (Giknis and Clifford, 2006); however, the values were within historical control ranges for the performing laboratory. Amylase (AMYL) levels were decreased in the 185 mg/kg-day group (0.8 fold; $p=0.013$). Alanine aminotransferase (ALT) levels were elevated in the 370 mg/kg-day group (1.3 fold; $p=0.045$). Glucose was elevated in the 741 mg/kg-day group (1.9 fold; 0.037). Glucose values for all groups were above reported normal values, however, only the glucose levels for the 741 mg/kg-day group were above the historical control ranges for the performing laboratory.

Blood sodium (0.95 and 0.97 fold; $p=0.007$ and $p=0.037$, respectively) and chloride (0.91 and 0.94 fold; $p=0.002$ and $p=0.004$, respectively) were decreased in the 370 and 741 mg/kg-day groups. These reduced chloride levels were below published and historical control ranges. These reduced sodium values were within published normal ranges, however, the values for the control group were above normal ranges. All sodium levels were within historical ranges for the performing laboratory. Potassium levels were decreased in all sodium periodate treatment groups (0.8, 0.9, 0.8, 0.8, and 0.8 fold; $p=0.010$, $p=0.140$, $p=0.004$, $p=0.008$, and $p=0.016$). Potassium levels for both treated and control groups were above published normal ranges, but were within historical control ranges. Phosphorous (PHOS) levels were increased in the 370 mg/kg-day group (1.1 fold; $p=0.007$) compared to the control. Phosphorous levels for both treated and control groups were above both published normal ranges and historical control ranges for the performing laboratory. Blood urea nitrogen (BUN) in males in the 185, 370 and 741 mg/kg-day groups exceeded the normal range and were elevated relative to the control (1.4, 5.1 and 2.2 fold, respectively); however, the 185 mg/kg-d group did not differ from the control group ($p=0.423$, $p=0.001$ and $p=0.027$, respectively). Creatinine (CREA) levels exceeded the normal range and were increased relative to the control group only in the 370 mg/kg-day sodium periodate group (1.7 fold; $p=0.033$). Albumin (ALB) levels were slightly decreased in all sodium periodate treatment groups (0.9, 0.9, 0.9, 0.9, and 0.9 fold, respectively) relative to the control group; however, the 370 mg/kg-day group did not differ from the control group ($p=0.018$, $p=0.039$, 0.001, $p=0.372$, and $p=0.004$, respectively). Albumin levels for both treated and control groups were below published normal ranges, but were within historical control ranges. Globulin (GLOB) levels were increased in the 741 mg/kg-day sodium periodate group (1.1 fold; $p=0.027$), but were within control ranges. See Appendix K for details.

6.3.8 Hematology

6.3.8.1 Females

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Neutrophil count and percent neutrophils were increased, relative to the control group, in 318 mg/kg-day sodium periodate group (4.1 and 4.3 fold; $p<0.001$ and $p<0.001$, respectively). Neutrophil count and percent neutrophils exceeded normal ranges in both the 159 and 318 mg/kg-day groups, however, the 159 mg/kg-day group did not differ from the concurrent control group. Lymphocyte counts and percent lymphocytes were decreased, relative to the control group, in the 318 mg/kg-day sodium periodate group (0.3 and 0.4 fold; $p<0.001$ and $p<0.001$, respectively). Lymphocyte counts and percent lymphocytes were also below normal ranges in both the 159 and 318 mg/kg-day groups, however, the 159 mg/kg-day group did not differ from the concurrent control group. Eosinophil count and percent eosinophils were below normal ranges and were decreased relative to the control group in the 318 mg/kg-day group (0.7 and 0.5 fold; $p=0.012$ and $p=0.001$, respectively). Conversely, percent eosinophils was increased in the 40 mg/kg-day group (1.7 fold; $p=0.009$), however, this value was within normal ranges.

Red blood cell counts (RBC) and percent hematocrit (HCT) were below normal ranges in females in the 80, 159, and 318 mg/kg-day sodium periodate groups. These values were also reduced approximately 0.9 fold compared to the control, however, this reduction was not statistically significant. Red cell distribution width (RDW) was increased in females in the 318 mg/kg-day group (1.1 fold; $p=0.001$). See Appendix L for details.

6.3.8.2 Males

White blood cell counts (WBC) were slightly above published normal ranges in the 370 and the 741 mg/kg-day sodium periodate groups (1.3 and 1.3 fold, respectively), but were not increased relative to the control group. Neutrophil count and percent neutrophils exceeded normal ranges and were increased relative to the control group in the 185 (2.1 and 2.1 fold; $p=0.034$ and $p=0.002$, respectively), 370 (6.5 and 4.9 fold; $p=0.001$ and $p=0.001$, respectively), and 741 mg/kg-day sodium periodate groups (5.5 and 3.9 fold; $p=0.007$ and $p=0.002$, respectively). Lymphocyte counts and percent lymphocytes were below normal ranges and were decreased relative to the control group in the 185 (0.7 and 0.8 fold; $p=0.041$ and $p=0.001$, respectively), 370 (0.3 and 0.2 fold; $p=0.001$ and $p=0.001$, respectively), and 741 mg/kg-day sodium periodate groups (0.3 and 0.3 fold; $p=0.002$ and $p=0.002$, respectively). Lymphocyte count was also below normal ranges in the 47 and 93 mg/kg-day groups, however, these dose groups did not differ from the concurrent control group. Eosinophil count and percent eosinophils were below normal ranges and were decreased relative to the control group in the 370 (0.6 and 0.5 fold; $p=0.051$ and $p=0.032$, respectively), and 741 mg/kg-day sodium periodate groups (0.6 and 0.4 fold; $p=0.111$ and $p=0.027$, respectively). However, the sodium periodate treated groups differed from the control groups only for the percent eosinophil parameter. Percent basophils was decreased in the 370 mg/kg-day group (0.3 fold; $p=0.002$). Basophil count was similarly decreased relative to the control (0.5 fold) in the 370 mg/kg-day group. Basophil parameters were within historical control ranges for the performing laboratory.

Red blood cell counts (RBC), hemoglobin (HGB), and percent hematocrit (HCT) were reduced relative to the control (0.9, 0.9, and 0.9 fold, respectively; $p=0.002$, $p<0.001$, and $p<0.001$). The RBC and HGB values were below published normal ranges while HCT was within both published normal ranges and laboratory historic control values. Additionally, RBC was below normal ranges and reduced, relative to the control group, in the 93 mg/kg-day dose group (0.9 fold; $p=0.041$).

Mean cell hemoglobin concentration (MCHC) was slightly above normal ranges in males in the 185, 370, and 741 mg/kg-day groups; however, MCHC was only elevated relative to the control group in the 370, and 741 mg/kg-day groups (1.02 and 1.05 fold; $p=0.043$ and $p=0.003$, respectively). In the 741 mg/kg-day group, mean cell volume (MCV) was slightly reduced (0.9 fold; $p=0.027$), red cell

distribution width (RDW) was slightly increased (1.1 fold; $p=0.020$), and mean platelet volume (MPV) was slightly increased (1.2 fold; $p=0.020$). See Appendix L for details.

6.3.9 Thyroid Hormone Analyses

6.3.9.1 Females

Serum T_4 levels ranged from 2.50 to 3.52 micrograms per deciliter ($\mu\text{g/dl}$) and serum TSH levels ranged from 2.05 to 3.82 nanograms per milliliter (ng/ml) in female rats. Serum T_4 and TSH levels did not differ between the control group and sodium periodate treatment groups. Serum T_3 levels ranged from 0.420 to 0.651 ng/ml and generally decreased with increasing dose. Serum T_3 levels were decreased compared to the control in females in the 318 mg/kg-day sodium periodate group (0.7 fold; $p=0.002$) and were outside of previously reported control values for the species (Chang et al., 2008; Christian and Trenton, 2003). See Appendix M for details.

6.3.9.2 Males

Serum T_4 levels ranged from 1.81 to 4.38 micrograms per deciliter ($\mu\text{g/dl}$), T_3 levels ranged from 0.225 to 0.614 nanograms per milliliter (ng/ml), and TSH levels ranged from 1.70 to 4.00 ng/ml in male rats. Serum T_4 , T_3 , and TSH levels were decreased compared to the control in males in the 370 (0.5, 0.4, and 0.5 fold; $p=0.001$, $p=0.005$, and $p=0.016$, respectively) and 741 mg/kg-day sodium periodate groups (0.6, 0.5, and 0.4 fold; $p=0.002$, $p=0.011$, and $p=0.005$, respectively). Serum T_3 levels were also reduced, relative to the control, in the 185 mg/kg-day group (0.7 fold; $p=0.015$). These serum T_4 , T_3 , and TSH levels were outside of previously reported control values for the species (Chang et al., 2008; Christian and Trenton, 2003). See Appendix M for details.

6.4 Determination of BMD and BMDL₁₀

Increased serum cholesterol was identified as the critical endpoint in this study based on the dose-related response in males and females as well as the association of this indicator of hepatic toxicity with other endpoints indicating adverse effects on the liver and kidney. Increased serum cholesterol is also associated with kidney toxicity and uremia (Keane et al., 2013; Moestrup and Nielsen, 2005). Hyperlipidemia associated with kidney toxicity and uremia may involve impairment of the lipid clearance capacity of the kidneys (Moestrup and Nielsen, 2005) and/or lipoprotein and hepatic lipase deficiencies mediated by hyperparathyroidism (Kraemer et al., 1982; Sato et al., 2002; Vaziri and Liang, 1996; Vaziri et al., 1997). Increased relative liver mass was observed in females and histopathological lesions (*i.e.*, liver necrosis) were noted in a few individuals of both sexes. Histopathologic evidence of kidney toxicity (*i.e.*, necrosis) and other serum (*e.g.*, increased BUN and CREA) and urine (*e.g.*, urine volume) markers of uremia were present in high dose groups. These endpoints were not modeled as they did not demonstrate a clear dose-response and the effects were only evident in higher dose groups (Barnes and Dourson 1988, EPA 2002). Benchmark Dose Software (BMDS v.2.5) was used to fit mathematical models to the serum cholesterol data for females and males separately and calculate a lower-bound confidence limit on a dose corresponding to a 10 percent response rate (BMDL₁₀) (EPA 1995, EPA 2000). The exponential 4, exponential 5, and Hill models were selected based on goodness-of-fit and statistical parameters ($p>0.1$, lowest AIC values and residuals). Mean BMDs of 33.3 and 55.2 mg/kg-day were calculated for females and males, respectively, based on the results of these three models. This corresponded to BMDL₁₀ of 17.2 and 33.7 mg/kg-day for females and males, respectively. See Appendix O for details.

6.5 Standing Operating Procedure and Protocol Deviations

The following deviations occurred during the study but were not considered to have compromised the integrity or validity of the study results:

Per the protocol, animal room temperature was to be maintained between 68 and 72 °F and humidity between 30 and 70%. However, on 31 July 2014 humidity in the animal room was 73-92% and the temperature was 73-76 °F from approximately 1030 to 1245 hours. The room temperature was additionally out of range on 3 August from approximately 1015 to 1100 (73 °F). These deviations were not reported to the PI. SOPs 011 and 008 which included provisions for notification and documentation in the event an animal room is out of compliance were not followed.

7 Discussion

Sodium and potassium periodate have been identified as potential replacements for perchlorate for use as oxidizers in military incendiary devices (Ball, 2012; Fields, 2012; Moretti et al., 2012). The use of perchlorate has been associated with environmental impacts and health hazards including thyroid dysfunction and developmental abnormalities. Based on structure activity relationships, munitions developers predicted sodium and potassium periodate to be less toxic than the oxidizers currently in use. The main objective of this study was to investigate the acute and subacute oral toxicity of sodium and potassium periodate in rats.

Clinical signs of toxicity were observed in rats at doses of 560 mg/kg and greater of potassium periodate and at doses of 175 mg/kg and greater of sodium periodate in the acute phase of the study. These signs were similar to those observed following acute intraperitoneal or oral administration of potassium and sodium iodates (Webster et al., 1957). However, convulsions and paresis noted with iodates were not present with periodate salts. These clinical signs may have been cation-associated effects as the authors indicated that toxicity of the salts was apparent at higher doses. Oral doses of potassium large enough to overwhelm the renal excretory mechanisms can produce potassium toxicity which manifests with characteristic acute cardiovascular changes, general weakness, ascending paralysis, gastroenteritis, vomiting, paralytic ileus, local mucosal necrosis and potential perforation, polydipsia/polyuria, early renal tubular necrosis, and convulsions (Saxena, 1989). Sodium toxicity can result when an excessive amount of sodium is consumed but is unlikely to occur if drinking water is available and sodium-regulating mechanisms are intact. Clinical signs of sodium toxicity may include nausea, diarrhea, thirst, irritability, weakness, convulsions, coma, edema, tremors, hypertension, and tachycardia. The oral LD₅₀s for potassium chloride and sodium chloride in rats (2600 and 3000 mg/kg, respectively) (HSDB, 2014a, b) are approximately four times those of the periodate salts, which suggests the toxicity observed for the periodate salts was due to the periodate ion. Additionally, the LD₅₀s for the two periodate salts were very similar in males (685 and 741 mg/kg for potassium and sodium periodate, respectively) and in females for potassium periodate (732 mg/kg). This again suggests that the toxicity of these compounds was largely due to the periodate ion. In females, however, the LD₅₀ for sodium periodate was considerably lower than that of males and that of potassium periodate. This would suggest that females are more sensitive to the sodium cation or the periodate ion or both.

Although sodium and potassium iodate have similarly been shown to have nearly equivalent LD₅₀s, the toxicity of the iodate salts was the same for both sexes (Webster et al., 1957). This suggests that the differential toxicity in sodium periodate is due to females being more sensitive to the toxic effects of the periodate ion rather than the sodium cation. However, gender-related differences in

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sodium metabolism, concentration, and urinary excretion have been documented. These gender-related differences may be associated with differences in regulation of arginine vasopressin (AVP) and the renin-angiotensin system (Crofton and Share, 1989; Miller et al., 1999; Rands et al., 2012; Stachenfeld et al., 2001). Males have higher plasma and/or urinary vasopressin levels, secretion of vasopressin is more sensitive to osmotic stimuli (e.g., hypertonic saline) in males, and the male kidney is more sensitive to vasopressin (Perucca et al., 2007). These differences lead to males being more susceptible to hypernatremia-induced hypertension, cardiovascular disease, and chronic kidney disease, whereas females are uniquely susceptible to hyponatremia-associated decreases in cerebral perfusion (Grikinienė et al., 2004; Perucca et al., 2007). Although these gender-related differences may have contributed to the apparently more severe renal toxicity observed in males in the subacute study, their role in the differential sensitivity of females to sodium periodate in the acute study remains unclear.

As female sensitivity to sodium periodate was not observed in the subacute study (i.e., toxicity was observed in males and females at approximately equivalent doses), female sensitivity may have been due to their prandial state. Because periodate is reduced to iodate and subsequently to the less toxic iodide (Anghileri, 1965; Taurog et al., 1966), the presence of food in the intestinal tract to serve as a reducing substrate may decrease the toxicity of periodate and iodate when exposure occurs orally (Webster et al., 1957). Although both males and females were fasted prior to the acute study, overnight fasting is typically more effective in emptying the gastric contents in female than male rats. This reduction in toxicity in the presence of food was apparent in the difference in sodium periodate toxicity between fasted rats (LD₅₀ 318 mg/kg) and fed rats (ALD 1431 mg/kg). However, a similar gender-related difference in toxicity would be expected in the potassium periodate acute study if the higher acute toxicity of sodium periodate in females were due to the periodate ion. In mice orally exposed to iodate salts, damage to the parietal cells of the stomach ranging from slight pyknosis to frank necrosis and exfoliation were attributed to direct contact of the iodate with the glandular cells (Webster et al., 1957). Similar effects were observed with subacute exposure to sodium periodate such that epithelial cell ulcer/erosion, necrosis, hemorrhage, and inflammation were noted in the stomach and inflammation and hemorrhage were noted in the small and large intestines of exposed rats. These degenerative changes likely disturbed the electrolyte balance as impaired salt and water absorption have been described in the diseased colon (Sandle, 1998). Inflamed intestinal mucosa have increased electrical conductance and permeability to monovalent ions and decreased Na⁺, K⁺-ATPase activity, resulting in a loss of the lumen negative potential difference and impaired sodium and chloride absorption (Sandle, 1998). It may be that the effects of gastric and intestinal mucosal contact with sodium periodate disrupted electrolyte transport possibly resulting in hyponatremia. Neurological effects associated with hyponatremia, including passive water influx in the brain, edema, hyper excitability, and epileptic activity, occur more frequently in females (Grikinienė et al., 2004; Kozniowska et al., 2008). Although speculative, as histopathology was not conducted for the acute study, it may be that the differential sensitivity to sodium periodate observed in females in the acute study was due to hyponatremia-associated morphological changes in the brain (e.g., perivascular edema or blood-brain barrier damage) resulting from higher levels of direct contact of sodium periodate with gastric mucosa due to the fasting state.

Although the oral toxicity of iodates and periodates is reduced in the presence of food and the toxicity of iodates administered in drinking water (i.e., in divided doses) is greatly reduced (Webster et al., 1959), there is a limit beyond which food cannot offer protection. Repeated oral exposure to sodium periodate resulted in mortalities in females at 318 mg/kg-day after 8 doses and in males at 185, 370 and 741 mg/kg-day after 13, 8, and 4 doses, respectively. As with iodate salts, these mortalities were likely attributable to kidney toxicity, uremia, and associated secondary effects (Webster et al., 1957). Subacute exposure to sodium periodate resulted in reduced body mass and

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body mass gain in female and male rats in the highest dose groups (80, 159, and 318 mg/kg-d and 185, 370, and 741 mg/kg-d, respectively). The reduced body mass may have been due in part to hypophagia as total food consumption was reduced in the high dose females and the 185 mg/kg-day males. However, feed conversion efficiency was also reduced in female and male dose groups exhibiting reduced body mass. The reduced feed conversion efficiency was likely due to the gastrointestinal effects associated with sodium periodate exposure. In mice orally exposed to iodate salts, damage to parietal cells, suppression of hydrochloric acid secretion, increased alkaline mucous secretion, increased stomach pH, and delayed gastric emptying were observed. Fatty visceral changes in iodate exposed mice were attributed reduced nourishment due to anorexia or delayed gastric emptying (Webster et al., 1957). Similar effects were observed with periodates such that thick mucus secretions were often noted in the stomach and the intestinal tracts were frequently empty or contained only yellow fluid. Additionally, histopathology demonstrated epithelial cell ulcer/erosion, necrosis, hemorrhage, and inflammation in the stomach and inflammation and hemorrhage in the small and large intestines of exposed rats, suggesting malabsorption may have contributed to the reduced food conversion efficiency.

The decreased body mass, body mass gain, and food consumption were part of an assemblage of effects exhibited by female and male rats exposed to high doses of sodium periodate that are hallmarks of the stress response (Everds et al., 2013). Subacute exposure to sodium periodate resulted in decreased mass of the thymus and spleen, thymocyte depletion in the thymus and spleen, altered leukocyte counts, and possible altered reproductive function (decreased mass of the ovaries and epididymides). Whether these effects are due solely to stress, are a secondary stress response to primary test-article related effects, or are direct test article effects is difficult to discern (Herzyk and Bussiere, 2008). Leukocyte differentials and mass of the adrenals and thymus are generally considered the most sensitive indicators of stress (Everds et al., 2013). Both females and males exhibited a stress leukogram (neutrophilia, lymphopenia, and monocytosis); however, the decrease in thymus mass was only significant for males and neither sex showed an increase in adrenal mass or adrenal hyperplasia. In the absence of evidence of effects on the adrenal gland, the role of stress in the effects on the immune, hematologic, and reproductive systems is unclear, suggesting test-article related effects. The lack of an increase in adrenal mass may have resulted from hypothyroid-associated adrenal mass decreases (Tohei, 2004; Tohei et al., 1997; Tohei et al., 1998).

Sodium periodate exposure caused decreased peripheral T_3 (females and males) and T_4 levels (males). While chronic stress is often associated with decreased T_3 and, in severe cases, decreased T_4 , stress induced hypothyroidism is present without altered TSH levels (Everds et al., 2013). Contrary to this and the expected pattern for hypothyroidism, the sodium periodate induced hypothyroidism was present with reduced TSH levels. This is also in contrast to the legacy incendiary oxidizer, ammonium perchlorate. Ammonium perchlorate administered to male and female rats at doses as low as 10 mg/kg-day for 14 days caused increased thyroid mass (Siglin et al., 2000; Yu et al., 2002) and follicular cell hypertrophy with microfollicle formation and colloid depletion (Siglin et al., 2000). The effects of ammonium perchlorate on the thyroid are mediated by inhibition of uptake of iodide as perchlorate competes for uptake into the thyroid by the NIS (Yu et al., 2002). Serum T_3 and T_4 are decreased and TSH levels increased in response to the decreased iodide uptake. Increased TSH levels result in shrinkage of thyroid follicle colloid area and increased cell height. If sustained, high TSH levels result in follicular cell hypertrophy/hyperplasia (Capen, 1997; Capen and Martin, 1989). Although T_3 / T_4 were reduced in sodium periodate treated rats, TSH was decreased rather than increased and follicle cell height did not differ with sodium periodate treatment. The condition of decreased T_3 and T_4 levels with normal or reduced TSH levels has been documented in the uremic rat model (Lim et al., 1980a). In the present study, both male and female rats in the sodium periodate dose groups with decreased thyroid hormone levels

also exhibited indications of uremia or kidney failure (e.g., increased BUN and creatinine, clinical observations of blood in the urine, polydipsia, polyuria, and acute tubular necrosis and hyaline droplets in renal tubular epithelium). The reason for the decrease in TSH with uremia is unclear, but may be due to pituitary disturbances including impaired response to thyrotropin-releasing hormone (TRH) and altered feedback regulation (Iglesias and Diez, 2009; Lim et al., 1980a). Although thyroid enlargement, nodules, and carcinoma are more common in patients with uremia/chronic kidney disease (Iglesias and Diez, 2009; Mariani and Berns, 2012), sodium periodate-induced uremia did not lead to increased thyroid mass or altered thyroid histology. However, longer duration exposures might produce these effects.

Many of the effects on endpoints measured in the subacute study may well be secondary to kidney toxicity and uremia. In the presence of renal failure, kidney functions including hormone production and secretion, acid-base homeostasis, fluid and electrolyte regulation, and waste-product elimination are impaired and abnormalities, such as anemia, acidemia, electrolyte imbalance, malnutrition, cardiovascular disease, endocrine abnormalities, and immune impairment can occur. Although overt anemia was not apparent, male rats in the mid-dose groups had decreased RBC and hemoglobin concentration. The electrolyte imbalance present in high dose groups, particularly males, consisted of reductions in sodium, potassium, and chloride levels. Although hyperkalemia is often associated with uremia, this typically occurs with oliguria and anuria in end stage renal disease (ESRD). Potassium depletion may occur due to renal potassium wasting and the kaliuretic effects of acidosis (Aiello and Moses, 2012). The malnutrition, as evidenced by reductions in body mass and body mass gain, associated with sodium periodate were more likely due to direct compound-related effects on the gastrointestinal system as described previously. There was no evidence of effects on the heart (e.g., heart mass with body mass covariate and histopathology).

Renal failure is also associated with endocrine abnormalities, including elevated estrogen and luteinizing hormone levels, reduced testosterone levels, and decreased spermatogenesis in males (Distiller et al., 1975; Handelsman and Dong, 1993). In females, anovulation due to reduced surges in luteinizing hormone is observed with uremia (Handelsman and Dong, 1993; Lim et al., 1980b). In the present study, reproductive hormones were not measured. Testicular degeneration and reduced epididymal mass in males and reduced ovarian mass were observed in the same dose groups exhibiting kidney effects, suggesting that the effects on the reproductive system may be secondary to effects on the renal system. Although stress may contribute to reduced reproductive function, testicular degeneration does not typically occur in rats in response to stress (Everds et al., 2013).

Effects on the immune system associated with kidney disease are characterized by activation of the innate immune system including increases in monocytes, macrophages, and granulocytes, coupled with immune deficiency caused by depletion of T- and B-lymphocytes (Hauser et al., 2008; Kato et al., 2008; Vaziri et al., 2012). Although female and male rats in higher sodium periodate dose groups exhibited neutrophilia and lymphopenia consistent with secondary effects of uremia, activation of the remaining granulocyte populations (i.e., monocytes and basophils) was not apparent. Mild eosinopenia was apparent, making the overall pattern more indicative of a stress leukogram. Histopathologic signs in the thymus and spleen suggest that the effects on the immune system are not due solely to stress. Because the thymus is sensitive to stress, stress-related changes are generally less consistent and less pronounced in the spleen relative to the thymus (Everds et al., 2013). Particularly in females, the effects on the spleen (i.e., reduced mass and white pulp atrophy) were more pronounced than the effects on the thymus (i.e., reduced mass and thymocyte apoptosis). More pronounced and/or consistent effects on a less sensitive organ suggest that the effects are not attributable to stress. Whether these effects are attributable to primary sodium periodate toxicity or secondary to uremia is unclear. Additional immunotoxicity

testing is warranted (e.g., an evaluation of bone marrow, an *in vivo* antigen challenge test, and spleen and thymus cellularity).

Two organ systems, gastrointestinal and hepatic, demonstrated compound-toxicity that was unrelated to uremia. In the stomach, treatment-related changes consisted of mucosal (epithelial cell) ulcer/erosion, areas of necrosis, hemorrhage, or inflammation. In the small and large intestines, inflammation, hemorrhage, or mononuclear cell infiltrate were present in higher dose groups. These effects can be attributed to the direct oxidation damage of sodium periodate on the mucous membranes and epithelium. The slight increase in liver mass in females in higher sodium periodate dose groups may indicate an adaptive response as liver enzymes were only mildly increased and in some instances were decreased (ALKP in females). However, a few animals in higher dose groups had substantial areas of hepatocellular necrosis. Serum cholesterol levels were increased in nearly all dose groups, which may further indicate hepatotoxicity or may be secondary to kidney disease (Keane et al., 2013; Quaschnig et al., 2001; Shoji et al., 2001).

8 Conclusions

The acute oral toxicity of potassium periodate and sodium periodate was tested using the Sequential Stage-Wise Probit method. The LD₅₀ for potassium periodate was 732 mg/kg for females (confidence interval of 539-838 and slope of 13.4) and 685 mg/kg for males (95% confidence interval of 580-809 and slope of 10.6). The LD₅₀ for sodium periodate was 318 mg/kg for females (95% confidence interval of 292-347 and slope of 24.3) and 741 mg/kg for males (confidence interval of 704-779 and slope of 31.2).

In the subacute study, repeated administration of sodium periodate via oral gavage resulted in mortality in females in the 318 mg/kg-day group after 8 days and in males in the 185, 370 and 741 mg/kg-day groups after 13, 8, and 4 days, respectively. Clinical signs including lethargy, squinting, congested breathing, prostration, hunched posture, rough coat, bloody bedding in cage, bloody urination, dried red material on front paws, brown perianal staining, diarrhea, bloody discharge from nose when dosed, and barbering were noted in female rats in the 318 mg/kg-day group and male rats in the 185, 370, and 741 mg/kg-day groups.

A cascade of effects that was likely secondary to kidney toxicity and uremia was observed in female rats in the 318 mg/kg-day group and male rats in the 185, 370, and 741 mg/kg-day groups. Decreased mass of the ovaries and epididymides and testicular degeneration were observed in sodium periodate groups with signs of kidney toxicity. These groups also exhibited a pattern of decreased T₃ and T₄ in the presence of decreased rather than the expected increased TSH, a pattern associated with uremia. Effects on the immune system associated with kidney disease are characterized by activation of the innate immune system coupled with immune deficiency. Sodium periodate exposed rats exhibited both activation of the innate immune system and lymphocyte depletion; however, the pattern of effects was more indicative of a stress leukogram. Additionally, effects on the thymus and spleen (*i.e.*, decreased mass and atrophy) in the absence of adrenal hyperplasia suggest more direct effects on the immune system. Rats in high sodium periodate dose groups exhibited malnutrition as indicated by decreased body mass. In addition to being associated with kidney toxicity, body mass effects were associated with gross and histopathologic findings in the gastrointestinal tract (e.g., erosion/ulcer, necrosis, and hemorrhage) and may be related to effects on absorption. The reproductive and thyroid related endocrine abnormalities may be secondary to uremia, whereas immune system impairment and malnutrition may also be due to direct compound toxicity and stress. Additional direct compound toxicity was evident in the liver as increased mass, ALT, CHOL, and necrosis were noted in high dose sodium periodate groups. The

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increases in cholesterol, noted in all male sodium periodate dose groups and females given 40 mg/kg-day and greater, may be indicative of hepatotoxicity or may be a secondary indicator of renal toxicity. Increased cholesterol was identified as the critical endpoint in this study based on the dose-related response in males and females and was used to derive the BMDL₁₀s of 17.2 and 33.7 mg/kg-day for females and males, respectively.

9 Point of Contact


Questions pertaining to this report should be referred to Emily May Lent at DSN 584-3980, commercial 410-436-3980, or by e-mail: usarmy.apg.medcom-phc.mbx.tox-info@mail.mil.

Prepared By:



EMILY MAY LENT
Toxicologist
Toxicity Evaluation Program (TEP)

12 Nov 2014
Date



LEE C.B. CROUSE
Biologist
TEP


12 Nov 2014
Date

Approved By:



ARTHUR J. O'NEILL
Program Manager, TEP

12 Nov 2014
Date



MARK S. JOHNSON
Director, Toxicology Portfolio

17 Nov 2014
Date

Appendix A

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Appendix B

Quality Assurance Statement

Appendix B

Quality Assurance Statement

For: Toxicology Study No. S.0015656-13, Protocol No. 30-13-06-01, titled “Acute and Subacute Oral Toxicity of Periodate in Rats, July–August 2013”, the following critical phases were audited by the Quality Systems and Regulatory Compliance Office (QSARC), Quality Assurance Unit (QAU):

PRE IN-LIFE PHASE OF THE STUDY

Critical Phase Inspected/Audited	Date Inspected /Audited	Date Reported to Management/SD
Study Protocol Good Laboratory Practice Standards and Animal Care Review	5/23/2013	5/23/2013

IN-LIFE PHASE OF THE STUDY

Critical Phase Inspected/Audited	Date Inspected /Audited	Date Reported to Management/SD
Acute Study - Test System Receipt, Facilities, Husbandry, Veterinary Care and Enrichment.	07/17/2013	07/26/2013
Acute Study - Test Substance Preparation and Administration, Labeling and Post Dose Observations.	08/14/2013	08/22/2013
Acute Study - Animal Euthanasia, Necropsy & Gross Macroscopic Pathology Exam Procedures	08/14/2013	08/22/2013
Acute Study - Periodate Salt Selection and Sub-Study In-Life Endpoint Criteria Compliance	08/14/2013	08/22/2013
14 Day Repeated Dose Study - Test Substance Preparation and Administration, Labeling and Post Dose Observations.	08/14/2013	08/22/2013
14 Day Repeated Dose Study - Test System Facilities, Identification, Husbandry, Food & Water Supply & Enrichment	08/14/2013	08/22/2013
14 Day Repeated Dose Study - Urinalysis Specimen Collection Procedures	08/29/2013	09/10/2013
14 Day Repeated Dose Study - Compliance with Study Protocol Modification # 1	08/29/2013	09/10/2013
Necropsy Study Personnel Qualifications and Training Records Review	08/29/2013	09/12/2013
Final Study Endpoint Criteria Compliance	08/30/2013	09/12/2013
14 Day Repeated Dose Study - Audit of Necropsy Records Review and Good Documentation Procedures	09/05/2013	09/12/2013

POST IN-LIFE PHASE OF THE STUDY

Critical Phase Inspected/Audited	Date Inspected /Audited	Date Reported to Management/SD
14 day Repeated Dose Study - Necropsy Records Review and Good Documentation Practice Procedures	09/05/2013	09/12/2013

Appendix B

Quality Assurance Statement

For: Toxicology Study No. S.0015656-13, Protocol No. 30-13-06-01, titled "Acute and Subacute Oral Toxicity of Periodate in Rats, July–August 2013", the following critical phases were audited by the Quality Systems and Regulatory Compliance Office (QSARC), Quality Assurance Unit (QAU):

POST IN-LIFE PHASE OF THE STUDY (continued)

Critical Phase Inspected/Audited	Date Inspected /Audited	Date Reported to Management/SD
Contract Pathology Contributing Scientist Report Review	05/06/2014	05/19/2014
Final Study Report Good Laboratory Practice Standards Review	08/12/2014	08/12/2014
Study Raw Data Good Laboratory Practice Standards Review	08/12/2014	08/12/2014

Note 1: All findings were made known to the Study Director and the Program Manager at the time of the audit/inspection. If there were no findings during the inspection, the inspection was reported to Management and the Study Director on the date shown in the table.

Note 2: In addition to the study specific critical phase inspections listed here, general facility and process based inspection not specifically related to this study are done monthly or annually in accordance with QA Standard Operating Procedure.

Note 3: This report has been audited by the Quality Assurance Unit (QSARC), and is considered to be an accurate account of the data generated and of the procedures followed.



Michael P. Kefauver
Quality Assurance Specialist, QSARC

16 OCT 2014

Date

Appendix C

Archives and Study Personnel

C-1 Archives

All raw data, documentation, records, protocol, and a copy of the final report generated as a result of this study will be archived in room 1026, building E-2100, USAPHC, for a minimum of five (5) years following submission of the final report to the Sponsor. If the report is used to support a regulatory action, it shall, along with all supporting data, be retained indefinitely.

Records on animal receipt, diet, and facility environmental parameters will be archived by the Veterinary Medical Division, Toxicology Portfolio, for a minimum of five (5) years following submission of the final report to the Sponsor.

Some ancillary records pertaining to this study, such as instrument maintenance logs, animal room observation logs, etc., will not be archived until those logbooks have been completed. Once complete they will be archived in room 1026, building E-2100, USAPHC.

Wet tissues, histology slides, and paraffin blocks are stored in building E-5158.

C-2 Personnel

Management: Dr. Mark S. Johnson, Ph.D., Portfolio Director, Toxicology; Mr. Arthur J. O'Neill, Manager, Toxicity Evaluation Program (TEP); Dr. Michael J. Quinn, Ph.D., Manager, Health Effects Research Program (HERP).

Study Director: Dr. Emily May Lent, Ph.D., Toxicologist, TEP.

Quality Assurance: Michael P. Kefauver, Quality Assurance Specialist, Quality System Office.

Veterinary Support and Animal Care: Dawn C. Fitzhugh, DVM, LTC, VC; Robert Sunderland, Animal Health Technician; Rebecca Kilby, Animal Health Technician; Jason Williams, Animal Health Technician; Felicia Thomas, Animal Health Technician.

Pathology Lab Coordinator: Patricia A. Beall, Biologist, TEP

In-Life Support: Emily May Lent, Toxicologist, TEP; Lee C.B. Crouse, Biologist, TEP; Theresa L. Hanna, Biological Technician, TEP; Allison M. Jackovitz, Biologist, ORISE.

Necropsy: Patricia A. Beall, Biologist, TEP; Alicia A. Shiflett, Biological Technician, TEP; Lee C.B. Crouse, Biologist, TEP; Emily May Lent, Toxicologist, TEP; Theresa L. Hanna, Biological Technician, TEP; Allison M. Jackovitz, Biologist, ORISE; Wilfred C. McCain, Toxicologist, TEP; William S. Eck, Biologist, HERP; Michael J. Quinn, Biologist, HERP.

Clinical Chemistry: Matthew A. Bazar, Biologist, TEP; Mark R. Way, Biologist, TEP.

Archivist: Martha L. Thompson, Data Acquisition Specialist, TEP

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Appendix D

Clinical Observations

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Table D-1
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

Potassium Periodate Sequential Stage Wise Probit Clinical Observations
Female Rats

Animal No.	Weight	Dose (mg/kg)	Volume (ml)*	Date	Time	Clinical Sign	Onset	Recovery
13-0685	227.6	175	0.20	7/16/13	0830	no abnormalities observed		
13-0686	232.7	560	0.65	7/16/13	0832	no abnormalities observed		
13-0687	221.5	1792	1.99	7/16/13	0837	lethargic	0845	
13-0687						prostrate	0847	1000
13-0687						labored breathing	0849	
13-0687						squinting	0909	
13-0687						rough coat	0927	
13-0687						eyes dark	1315	
13-0687						MK	1425	
13-0688	206.8	2000	2.07	7/16/13	0839	squinting	0851	
13-0688						hunched posture	0856	
13-0688						rough coat	0927	
13-0688						lethargic	0927	
13-0688						labored breathing	0945	
13-0688						eyes dark	1315	
13-0688						FD	1415	
13-0698	194.1	750	0.97	7/18/13	0856	lethargic	0930	0640 on 7/19
13-0698						squinting	0930	0640 on 7/19
13-0698						hunched posture	1000	0640 on 7/19
13-0698						rough coat	1000	0640 on 7/19

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13-0699	204.9	750	1.03	7/18/13	0857	hunched posture	0923	
13-0699						lethargic	0923	
13-0699						squinting	0923	0640 on 7/19
13-0699						rough coat	1000	
13-0699						bloody urine	0640 on 7/19	
13-0699						MK	1045 on 7/19	
13-0700	203.5	750	1.02	7/18/13	0858	squinting	0924	
13-0700						lethargic	0924	
13-0700						hunched posture	0932	
13-0700						rough coat	1000	
13-0700						labored breathing	1020	
13-0700						prostrate	1045	
13-0700						MK	1130	
13-0701	199.7	1000	1.33	7/18/13	0901	lethargic	0924	
13-0701						diarrhea	0931	
13-0701						prostrate	0932	
13-0701						hunched posture	1000	
13-0701						rough coat	1000	
13-0701						FD	0645 on 7/19	
13-0702	208.4	1000	1.39	7/18/13	0902	lethargic	0924	
13-0702						squinting	0932	
13-0702						hunched posture	0932	
13-0702						rough coat	1000	

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13-0702						labored breathing	1020
13-0702						eyes dark	1045
13-0702						FD	0645 on 7/19
13-0703	209.8	1000	1.40	7/18/13	0904	lethargic	0933
13-0703						hunched posture	0933
13-0703						squinting	0933
13-0703						rough coat	1000
13-0703						FD	0645 on 7/19
13-0704	196.0	1300	1.70	7/18/13	0906	lethargic	0924
13-0704						squinting	0924
13-0704						prostrate	0924
13-0704						rough coat	0934
13-0704						labored breathing	0934
13-0704						diarrhea	1020
13-0704						MK	1315
13-0705	202.6	1300	1.85	7/18/13	0908	lethargic	0925
13-0705						hunched posture	0925
13-0705						squinting	0925
13-0705						rough coat	1020
13-0705						labored breathing	1020
13-0705						FD	0645 on 7/19
13-0706	209.4	1300	1.90	7/18/13	0910	lethargic	0925
13-0706						prostrate	0925

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13-0706						squinting	0925	
13-0706						rough coat	1000	
13-0706						labored breathing	1020	
13-0706						FD	1034	
13-0677	205.4	560	1.15	7/23/13	0747	squinting	0815	1405
13-0677						hunched posture	0815	0635 on 7/24
13-0677						lethargic	0853	1405
13-0677						rough coat	0853	1222
13-0678	217.0	560	1.22	7/23/13	0749	squinting	0815	1035
13-0678						hunched posture	0815	0635 on 7/24
13-0678						lethargic	0853	1035
13-0679	203.1	650	1.32	7/23/13	0750	squinting	0815	
13-0679						hunched posture	0815	0842
13-0679						lethargic	0842	
13-0679						prostrate	0842	1035
13-0679						hunched posture	1035	
13-0679						red discharge from nose	1405	
13-0679						FD	0635 on 7/24	
13-0758	226.2	650	1.47	7/23/13	0752	red discharge from nose	0815	0635 on 7/24
13-0758						hunched posture	0853	0635 on 7/24
13-0758						squinting	0853	0635 on 7/24
13-0758						lethargic	0853	0635 on 7/24
13-0759	220.8	650	1.44	7/23/13	0754	hunched posture	0815	7/24
13-0759						squinting	0840	1405

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13-0759						lethargic	0939	7/24
13-0760	221.8	860	1.91	7/23/13	0755	hunched posture	0815	7/24
13-0760						squinting	0844	7/24
13-0760						lethargic	0854	7/24
13-0761	217.7	860	1.87	7/23/13	0757	prostrate	0845	1035
13-0761						lethargic	0845	
13-0761						squinting	0845	
13-0761						hunched posture	1035	
13-0761						FD	0635 on 7/24	
13-0762	210.7	860	1.81	7/23/13	0758	prostrate	0845	1225
13-0762						lethargic	0845	
13-0762						squinting	0845	
13-0762						rough coat	0939	
13-0762						hunched posture	1225	1405
13-0762						prostrate	1405	
13-0762						labored breathing	1510	
13-0762						FD	0635 on 7/24	

***Concentration:** 200 mg/ml (7/16/13), 150 mg/ml (7/18/13), 100 mg/ml (7/23/13)

Table D-2
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

Potassium Periodate Sequential Stage Wise Probit Clinical Observations
Male Rats

Animal No.	Weight	Dose (mg/kg)	Volume (ml)*	Date	Time	Clinical Sign	Onset	Recovery
13-0651	306.8	175	0.27	7/16/13	0820	no abnormalities observed		
13-0652	319.1	560	0.89	7/16/13	0822	lethargic	0843	0945
13-0652						rough coat	0957	1315
13-0653	305.1	1792	2.73	7/16/13	0824	lethargic	0843	
13-0653						labored breathing	0904	
13-0653						laying on side	0904	0958
13-0653						legs stiff	0904	0958
13-0653						rough coat	0904	
13-0653						prostrate	0958	1110
13-0653						eyes dark	1315	
13-0653						MK	1437	
13-0654	296.4	2000	2.96	7/16/13	0826	lethargic	0843	
13-0654						squinting	0904	
13-0654						prostrate	0904	0945
13-0654						rough coat	0917	
13-0654						labored breathing	0919	
13-0654						eyes dark	1315	
13-0654						MK	1420	
13-0665	325.7	750	1.63	7/18/13	0841	lethargic	0918	

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13-0665						squinting	0918	
13-0665						rough coat	0918	
13-0665						labored breathing	0926	
13-0665						eyes dark	0928	
13-0665						FD	0640 on 7/19	
13-0666	283.8	750	1.42	7/18/13	0842	lethargic	0918	0645 on 7/19
13-0666						hunched posture	0918	0645 on 7/19
13-0666						squinting	0926	0645 on 7/19
13-0666						rough coat	0926	0645 on 7/19
13-0666						eyes dark	0928	0645 on 7/19
13-0666						nose swollen/red	7/20	7/22
13-0666						slightly lethargic	7/20	7/22
13-0667	296.6	750	1.49	7/18/13	0844	lethargic	0918	0645 on 7/19
13-0667						hunched posture	0918	0645 on 7/19
13-0667						squinting	0926	0645 on 7/19
13-0667						eyes dark	0928	0645 on 7/19
13-0667						rough coat	0645 on 7/19	7/20
13-0667						slightly lethargic	7/20	7/22
13-0668	314.0	1000	2.09	7/18/13	0846	lethargic	0918	
13-0668						hunched posture	0918	
13-0668						labored breathing	0926	
13-0668						squinting	0926	
13-0668						rough coat	0958	

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13-0668						FD	0640 on 7/19
13-0669	288.4	1000	1.92	7/18/13	0848	lethargic	0918
13-0669						laying on side	0918 0958
13-0669						squinting	0926
13-0669						eyes dark	0926
13-0669						hunched posture	0958
13-0669						rough coat	1045
13-0669						diarrhea	1330
13-0669						FD	0640 on 7/19
13-0670	322.5	1000	2.15	7/18/13	0849	lethargic	0920
13-0670						prostrate	0920
13-0670						squinting	0920
13-0670						labored breathing	0930
13-0670						rough coat	1000
13-0670						diarrhea	1045
13-0670						FD	0640 on 7/19
13-0671	336.2	1300	2.91	7/18/13	0851	lethargic	0920
13-0671						squinting	0920
13-0671						hunched posture	0920
13-0671						rough coat	0930
13-0671						diarrhea	1000
13-0671						FD	0645 on 7/19

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13-0672	321.6	1300	2.79	7/18/13	0852	lethargic	0920	
13-0672						prostrate	0920	
13-0672						squinting	0920	
13-0672						diarrhea	1000	
13-0672						rough coat	1000	
13-0672						eyes dark	1020	
13-0672						MK	1138	
13-0673	330.1	1300	2.86	7/18/13	0853	lethargic	0922	
13-0673						prostrate	0922	0640 on 7/19
13-0673						labored breathing	0930	0640 on 7/19
13-0673						squinting	1000	0640 on 7/19
13-0673						rough coat	1045	7/22
13-0673						hunched posture	0640 on 7/19	
13-0673						chromodacryor rhea both eyes	7/20	
13-0673						squinting	7/22	
13-0673						swollen nose - red discharge	7/22	
13-0673						red material on left front paw	7/23	
13-0673						MK	1430 on 7/23	
13-0674	374.5	560	2.10	7/23/13	0802	no abnormalities observed		
13-0675	339.2	560	1.90	7/23/13	0803	prostrate	0855	0940
13-0675						lethargic	0855	0940
13-0675						squinting	0855	0940
13-0675						hunched posture	1002	

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13-0675						squinting	0635 on 7/24	
13-0675						FD	1115 on 7/24	
13-0676	335.1	650	2.18	7/23/13	0806	squinting	0845	
13-0676						hunched posture	0855	
13-0676						lethargic	0855	
13-0676						labored breathing	1510	
13-0676						diarrhea	0635 on 7/24	
13-0676						FD	0635 on 7/24	
13-0728	323.1	650	2.10	7/23/13	0807	hunched posture	0845	0830 on 7/24
13-0728						lethargic	0855	0830 on 7/24
13-0728						squinting	1035	0830 on 7/24
13-0729	294.4	650	1.91	7/23/13	0808	hunched posture	0845	0830 on 7/24
13-0729						squinting	0845	0830 on 7/24
13-0729						lethargic	1035	0830 on 7/24
13-0730	296.8	860	2.55	7/23/13	0810	hunched posture	0845	
13-0730						squinting	0845	
13-0730						lethargic	0855	
13-0730						rough coat	1405	
13-0730						FD	0635 on 7/24	
13-0731	288.5	860	2.49	7/23/13	0812	prostrate	0845	
13-0731						squinting	0845	
13-0731						lethargic	0855	

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13-0731						hunched posture	1405
13-0731						rough coat	1405
13-0731						FD	0635 on 7/24
13-0732	293.9	860	2.53	7/23/13	0814	hunched posture	0845
13-0732						prostrate	855
13-0732						lethargic	0855
13-0732						squinting	0855
13-0732						hunched posture	1003
13-0732						FD	0635 on 7/24

***Concentration:** 200 mg/ml (7/16/13), 150 mg/ml (7/18/13), 100 mg/ml (7/23/13)

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Table D-3
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

Sodium Periodate Sequential Stage Wise Probit and Approximate Lethal Dose Clinical Observations
Female Rats

Animal No.	Weight	Dose (mg/kg)	Volume (ml)*	Date	Time	Clinical Sign	Onset	Recovery
13-0681	208.4	175	0.18 ^A	7/16/13	0806	hunched posture	0945	1110
13-0681						lethargic	0945	1110
13-0682	216.0	560	0.6 ^A	7/16/13	0809	squinting	0840	
13-0682						lethargic	0840	
13-0682						hunched posture	0909	1310
13-0682						rough coat	0945	
13-0682						red discharge from nose	1115	1510
13-0682						labored breathing	1310	1510
13-0682						FD	0640 on 7/17	
13-0683	220.2	1792	1.97 ^A	7/16/13	0812	squinting	0835	
13-0683						lethargic	0835	
13-0683						prostrate	0835	
13-0683						rough coat	0849	
13-0683						labored breathing	0853	
13-0683						eyes dark red	0857	
13-0683						diarrhea in cage	0905	
13-0683						FD	0905	
13-0684	220.9	2000	2.21 ^A	7/16/13	0815	squinting	0835	
13-0684						lethargic	0835	
13-0684						prostrate	0835	
13-0684						rough coat	0845	
13-0684						eyes dark red	0847	
13-0684						very pale skin	0902	
13-0684						FD	0905	
13-0680	213.7	400	0.86	7/18/13	0817	prostrate	0835	
13-0680						squinting	0835	
13-0680						lethargic	0835	
13-0680						labored breathing	0938	
13-0680						eyes dark red	0938	
13-0680						FD	0956	

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13-0689	234.6	400	0.94	7/18/13	0818	prostrate	0835	
13-0689						lethargic	0835	
13-0689						squinting	0835	
13-0689						rough coat	0938	
13-0689						eyes dark red	0956	
13-0689						diarrhea	0956	
13-0689						FD	1015	
13-0690	218.8	400	0.88	7/18/13	0820	lethargic	0835	
13-0690						squinting	0835	
13-0690						prostrate	0915	
13-0690						hunched posture	0938	
13-0690						rough coat	0955	
13-0690						labored breathing	1015	
13-0690						FD	0640 on 7/19	
13-0691	229.0	560	1.28	7/18/13	0823	lethargic	0835	
13-0691						laying on side	0835	0915
13-0691						labored breathing	0835	
13-0691						prostrate	0915	
13-0691						FD	0944	
13-0692	207.8	560	1.16	7/18/13	0824	lethargic	0915	
13-0692						squinting	0915	
13-0692						hunched posture	0915	
13-0692						rough coat	0940	
13-0692						eyes dark red	0940	
13-0692						labored breathing	0957	
13-0692						MK	1100	
13-0693	222.2	700	1.55	7/18/13	0826	lethargic	0835	
13-0693						squinting	0835	
13-0693						hunched posture	0835	
13-0693						rough coat	0915	
13-0693						diarrhea	1015	
13-0693						FD	0640 on 7/19	
13-0694	226.9	700	1.59	7/18/13	0827	lethargic	0835	
13-0694						squinting	0835	
13-0694						hunched posture	0835	
13-0694						rough coat	0940	
13-0694						labored breathing	0940	

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13-0694						FD	0640 on 7/19	
13-0695	264.7	700	1.86	7/18/13	0829	lethargic	0915	
13-0695						squinting	0915	
13-0695						prostrate	0915	
13-0695						rough coat	0940	
13-0695						diarrhea	0940	
13-0695						hunched posture	1007	
13-0695						FD	0640 on 7/19	
13-0696	219.1	875	1.92	7/18/13	0830	lethargic	0915	
13-0696						laying on side	0915	
13-0696						hunched posture	0940	
13-0696						squinting	0940	
13-0696						labored breathing	0940	
13-0696						rough coat	1007	
13-0696						FD	1304	
13-0697	208.5	875	1.83	7/18/13	0831	lethargic	0839	
13-0697						prostrate	0839	
13-0697						FD	0940	
13-0763	230.4	120	0.28	7/23/13	0819	no abnormalities observed		
13-0764	207.1	120	0.25	7/23/13	0822	no abnormalities observed		
13-0765	224.2	175	0.39	7/23/13	0823	squinting	0850	0635 on 7/24
13-0765						prostrate	0850	0858
13-0765						lethargic	0858	0945
13-0765						hunched posture	0858	0635 on 7/24
13-0766	218.9	175	0.38	7/23/13	0825	squinting	0850	1510
13-0766						hunched posture	1005	1510
13-0767	209.3	265	0.55	7/23/13	0827	squinting	1035	1510
13-0767						hunched posture	1035	0635 on 7/24
13-0767						lethargic	1035	0635 on 7/24
13-0768	229.0	265	0.61	7/23/13	0828	squinting	0850	0945
13-0768						lethargic	1005	0635 on 7/24
13-0768						hunched posture	1035	0635 on 7/24
13-0769	208.6	265	0.55	7/23/13	0830	hunched posture	1005	0635 on 7/24

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13-0769						squinting	1035	1510
13-0769						lethargic	1035	0635 on 7/24
13-0770	229.9	290	0.67	7/25/13	0807	laying on side	0837	1400
13-0770						squinting	0837	1400
13-0770						prostrate	0917	1400
13-0771	214.9	290	0.62	7/25/13	0809	hunched posture	0917	0635 on 7/26
13-0771						squinting	0917	0635 on 7/26
13-0772	237.7	290	0.69	7/25/13	0811	prostrate	0838	1400
13-0772						squinting	0838	
13-0772						laying on side	0917	1400
13-0772						hunched posture	1100	
13-0772						MK	0739 on 7/26	
13-0773	212.4	325	0.69	7/25/13	0814	prostrate	0838	1400
13-0773						squinting	0838	1400
13-0773						FD	0635 on 7/26	
13-0774	217.0	325	0.71	7/25/13	0817	hunched posture	0918	1400
13-0774						squinting	0918	1400
13-0775	212.7	325	0.69	7/25/13	0819	prostrate	0841	1400
13-0775						squinting	0841	1400
13-0775						hunched posture	1100	0635 on 7/26
13-0776	214.4	365	0.78	7/25/13	0822	prostrate	0842	
13-0776						squinting	0842	
13-0776						FD	1109	
13-0777	238.3	365	0.87	7/25/13	0824	prostrate	0918	1400
13-0777						squinting	0918	
13-0777						hunched posture	1100	
13-0777						FD	0900 on 7/26	
13-0778	223.9	365	0.82	7/25/13	0827	hunched posture	0918	
13-0778						squinting	0918	
13-0778						FD	1319	
13-0788	252.8	0	1.81	7/31/13	0722	no abnormalities observed		
13-0789	260.2	188	0.24	7/31/13	0724	no abnormalities observed		
13-0790	248.9	283	0.35	7/31/13	0726	lethargic	0905	1100
13-0791	226.6	424	0.48	7/31/13	0729	lethargic	0839	1100

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13-0791						hunched posture	0839	1100
13-0791						squinting	0905	1100
13-0792	252.5	636	0.80	7/31/13	0732	lethargic	0839	1100
13-0792						hunched posture	0839	1100
13-0793	247.0	954	1.18	7/31/13	0735	lethargic	0757	0900 on 8/1
13-0793						prostrate	0757	0900 on 8/1
13-0793						squinting	0757	0900 on 8/1
13-0793						rough coat	0840	0900 on 8/1
13-0793						hunched posture	0840	0900 on 8/1
13-0793						blood stained bedding	8/1	
13-0794	235.9	1431	1.69	7/31/13	0737	lethargic	0757	
13-0794						squinting	0757	
13-0794						prostrate	0757	
13-0794						labored breathing	0840	
13-0794						MK	0910	

***Concentration:** 200 mg/ml^A, 100 mg/ml

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Table D-4
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

Sodium Periodate Sequential Stage Wise Probit Clinical Observations
Male Rats

Animal No.	Weight	Dose (mg/kg)	Volume (ml)*	Date	Time	Clinical Sign	Onset	Recovery
13-0647	304.5	175	0.27 ^A	7/16/13	0746	lethargic	0908	0945
13-0647						squinting	0908	0945
13-0647						prostrate	0908	0945
13-0647						labored breathing	0908	0945
13-0648	285.1	560	0.8 ^A	7/16/13	0753	squinting	0835	0640 on 7/17
13-0648						lethargic	0835	0640 on 7/17
13-0648						hunched posture	0916	0945
13-0648						labored breathing	0945	1510
13-0648						rough coat	0945	0640 on 7/17
13-0648						red discharge from nose	1115	1510
13-0649	321.0	1792	2.88 ^A	7/16/13	0800	squinting	0810	
13-0649						lethargic	0810	
13-0649						prostrate	0810	
13-0649						rough coat	0845	
13-0649						eyes dark red	0849	
13-0649						labored breathing	0852	
13-0649						chromodacryorrhea	0906	
13-0649						diarrhea in cage	0915	
13-0649						FD	0915	
13-0650	297.6	2000	2.98 ^A	7/16/13	0803	lethargic	0810	
13-0650						prostrate	0810	
13-0650						squinting	0810	
13-0650						rough coat	0845	
13-0650						eyes dark red	0849	
13-0650						FD	0957	
13-0655	312.2	400	1.25	7/18/13	0746	squinting	0752	0640 on 7/19
13-0655						prostrate	0752	0640 on 7/19
13-0655						lethargic	0752	0640 on

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								7/19
13-0655						red discharge from nose	0754	0640 on 7/19
13-0655						dark eyes	0759	0640 on 7/19
13-0655						rough coat	0832	7/22
13-0655						hunched posture	0957	7/20
13-0655						red discharge from nose	1040	0640 on 7/19
13-0655						slightly lethargic	7/20	7/23
13-0656	317.2	400	1.27	7/18/13	0749	hunched posture	0759	0640 on 7/19
13-0656						lethargic	0800	
13-0656						prostrate	0805	1040
13-0656						labored breathing	0819	1040
13-0656						squinting	0832	0640 on 7/19
13-0656						rough coat	0935	
13-0656						dark eyes	0935	0640 on 7/19
13-0656						prostrate	0640 on 7/19	
13-0656						front paws clenched	0640 on 7/19	
13-0656						tip of nose swollen/red	0640 on 7/19	
13-0656						MK	1103 on 7/19	
13-0657	294.7	400	1.18	7/18/13	0752	lethargic	0807	0640 on 7/19
13-0657						squinting	0807	0640 on 7/19
13-0657						hunched posture	0811	1040
13-0657						labored breathing	0832	1040
13-0657						rough coat	0912	0640 on 7/19
13-0657						slightly lethargic	7/20	7/22
13-0657						dried red material on nose	7/23	
13-0658	300.2	560	1.68	7/18/13	0754	lethargic	0807	0640 on 7/19
13-0658						hunched posture	0912	0640 on 7/19
13-0658						rough coat	0935	7/22
13-0658						slightly lethargic	7/20	7/22
13-0659	307.8	560	1.72	7/18/13	0757	squinting	0811	0640 on 7/19
13-0659						lethargic	0811	7/22

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13-0659						prostrate	0811	0640 on 7/19
13-0659						labored breathing	0832	0954
13-0659						rough coat	1004	1240
13-0659						slightly lethargic	7/20	7/22
13-0659						dried red material on nose	7/20	7/22
13-0660	299.9	700	2.1	7/18/13	0800	lethargic	0820	0640 on 7/19
13-0660						squinting	0912	0640 on 7/19
13-0660						hunched posture	0912	1040
13-0660						labored breathing	0912	0954
13-0660						eyes dark red	0935	0640 on 7/19
13-0660						prostrate	1000	1040
13-0660						rough coat	0640 on 7/19	7/22
13-0660						abnormal gait - splayed and hunched	0640 on 7/19	7/20
13-0660						red/swollen nose	7/20	7/22
13-0661	307.6	700	2.16	7/18/13	0802	lethargic	0811	7/20
13-0661						hunched posture	0811	0640 on 7/19
13-0661						squinting	0820	0640 on 7/19
13-0661						labored breathing	0914	0640 on 7/19
13-0661						rough coat	0954	0640 on 7/19
13-0661						brown perianal staining	0640 on 7/19	7/20
13-0661						diarrhea	0640 on 7/19	7/20
13-0661						red material on nose/face	0640 on 7/19	7/20
13-0661						slightly lethargic	7/20	7/22
13-0662	334.2	700	2.34	7/18/13	0804	lethargic	0820	0640 on 7/19
13-0662						squinting	0820	0640 on 7/19
13-0662						prostrate	0832	1040
13-0662						labored breathing	0832	0640 on 7/19
13-0662						eyes dark red	0935	0640 on 7/19
13-0662						rough coat	1000	7/20
13-0662						slightly lethargic	7/20	7/22

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13-0663	307.5	875	2.7	7/18/13	0807	lethargic	0820	
13-0663						prostrate	0820	
13-0663						squinting	0820	
13-0663						rough coat	0832	
13-0663						labored breathing	0912	
13-0663						diarrhea	0935	
13-0663						eyes dark red	0935	
13-0663						FD	0640 on 7/19	
13-0664	298.9	875	2.62	7/18/13	0810	lethargic	0820	
13-0664						laying on side	0820	0832
13-0664						labored breathing	0820	
13-0664						squinting	0832	
13-0664						prostrate	0912	
13-0664						eyes dark red	0935	
13-0664						rough coat	0935	
13-0664						FD	0955	
13-0733	293.4	750	2.2	7/23/13	0832	squinting	0850	
13-0733						prostrate	0850	
13-0733						lethargic	0900	
13-0733						FD	0945	
13-0734	278.7	750	2.09	7/23/13	0834	prostrate	0850	
13-0734						lethargic	0900	
13-0734						squinting	0900	
13-0734						FD	0945	
13-0735	277.1	750	2.08	7/23/13	0836	prostrate	0850	
13-0735						lethargic	0850	
13-0735						squinting	0850	
13-0735						FD	0945	
13-0736	282.0	810	2.28	7/23/13	0837	hunched posture	0900	7/24
13-0736						squinting	0900	7/24
13-0736						lethargic	0945	
13-0736						rough coat	1415	
13-0736						chromodacryorrhea right eye	0830 on 7/24	7/25
13-0736						pale ears	7/24	7/25
13-0736						blood stained bedding	7/24	
13-0736						red discharge from nose	7/25	7/26

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13-0736						MK	on 7/26	
13-0737	295.6	810	2.4	7/23/13	0839	lethargic	0900	
13-0737						hunched posture	0945	
13-0737						squinting	1005	
13-0737						rough coat	1415	
13-0737						FD	0635 on 7/24	
13-0738	289.3	810	2.34	7/23/13	0840	lethargic	0900	0635 on 7/24
13-0738						hunched posture	0945	0635 on 7/24
13-0739	321.1	725	2.33	7/25/13	750	hunched posture	0755	
13-0739						labored breathing	0755	
13-0739						squinting	0759	
13-0739						prostrate	0832	
13-0739						FD	0927	
13-0740	313.6	725	2.28	7/25/13	752	hunched posture	0808	1400
13-0740						squinting	0915	1400
13-0741	317.6	725	2.31	7/25/13	754	hunched posture	0808	1400
13-0742	300.2	750	2.25	7/25/13	759	hunched posture	0808	
13-0742						squinting	0816	
13-0742						prostrate	0822	
13-0742						FD	0940	
13-0743	318.0	750	2.39	7/25/13	801	hunched posture	0822	1400
13-0743						laying on side	0834	1400
13-0744	288.0	750	2.16	7/25/13	803	laying on side	0836	
13-0744						squinting	0836	
13-0744						FD	0635 on 7/26	

***Concentration:** 200 mg/ml^A, 100 mg/ml

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Table D-5
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
Sodium Periodate 14-Day Clinical Observations
Female Rats

Animal No.	Dose Group*	Clinical Sign	Day of First Appearance	Day of Last Appearance
13-0799	Water Control	no abnormalities observed		
13-0800	Water Control	no abnormalities observed		
13-0811	Water Control	no abnormalities observed		
13-0812	Water Control	no abnormalities observed		
13-0815	Water Control	no abnormalities observed		
13-0816	Water Control	no abnormalities observed		
13-0821	Water Control	no abnormalities observed		
13-0822	Water Control	no abnormalities observed		
13-0831	Water Control	no abnormalities observed		
13-0832	Water Control	no abnormalities observed		
13-0823	20 mg/kg-day ^A	no abnormalities observed		
13-0824	20 mg/kg-day ^A	no abnormalities observed		
13-0833	20 mg/kg-day ^A	no abnormalities observed		
13-0834	20 mg/kg-day ^A	no abnormalities observed		
13-0835	20 mg/kg-day ^A	no abnormalities observed		
13-0836	20 mg/kg-day ^A	no abnormalities observed		
13-0841	20 mg/kg-day ^A	no abnormalities observed		

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13-0842	20 mg/kg-day ^A	no abnormalities observed		
13-0843	20 mg/kg-day ^A	no abnormalities observed		
13-0844	20 mg/kg-day ^A	no abnormalities observed		
13-0807	40 mg/kg-day ^B	soft feces	0	0
13-0808	40 mg/kg-day ^B	chromodacryorrhea right eye	13	13
13-0817	40 mg/kg-day ^B	no abnormalities observed		
13-0818	40 mg/kg-day ^B	no abnormalities observed		
13-0819	40 mg/kg-day ^B	no abnormalities observed		
13-0820	40 mg/kg-day ^B	no abnormalities observed		
13-0845	40 mg/kg-day ^B	no abnormalities observed		
13-0846	40 mg/kg-day ^B	no abnormalities observed		
13-0847	40 mg/kg-day ^B	no abnormalities observed		
13-0848	40 mg/kg-day ^B	no abnormalities observed		
13-0797	80 mg/kg-day ^C	no abnormalities observed		
13-0798	80 mg/kg-day ^C	no abnormalities observed		
13-0809	80 mg/kg-day ^C	no abnormalities observed		
13-0810	80 mg/kg-day ^C	wet chin	10	10
13-0810	80 mg/kg-day ^C	blood from nose when dosed	11	11
13-0827	80 mg/kg-day ^C	no abnormalities observed		
13-0828	80 mg/kg-day ^C	no abnormalities observed		
13-0851	80 mg/kg-day ^C	no abnormalities observed		
13-0852	80 mg/kg-day ^C	no abnormalities observed		

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13-0853	80 mg/kg-day ^C	no abnormalities observed		
13-0854	80 mg/kg-day ^C	no abnormalities observed		
13-0801	159 mg/kg-day ^D	no abnormalities observed		
13-0802	159 mg/kg-day ^D	no abnormalities observed		
13-0803	159 mg/kg-day ^D	no abnormalities observed		
13-0804	159 mg/kg-day ^D	chromodacryorrhea right eye	4	4
13-0829	159 mg/kg-day ^D	no abnormalities observed		
13-0830	159 mg/kg-day ^D	no abnormalities observed		
13-0837	159 mg/kg-day ^D	no abnormalities observed		
13-0838	159 mg/kg-day ^D	no abnormalities observed		
13-0849	159 mg/kg-day ^D	no abnormalities observed		
13-0850	159 mg/kg-day ^D	no abnormalities observed		
13-0795	318 mg/kg-day ^E	prostrate	1	1
13-0795	318 mg/kg-day ^E	squinting, lethargic	1	3
13-0795	318 mg/kg-day ^E	congested breathing, hunched posture	2	3
13-0795	318 mg/kg-day ^E	slightly congested breathing	4	14
13-0795	318 mg/kg-day ^E	slightly lethargic	4	13
13-0795	318 mg/kg-day ^E	squinting, hunched posture	6	8
13-0795	318 mg/kg-day ^E	hunched posture	10	13
13-0795	318 mg/kg-day ^E	squinting	12	13
13-0795	318 mg/kg-day ^E	prostrate	12	12
13-0795	318 mg/kg-day ^E	congested breathing	13	13

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13-0796	318 mg/kg-day ^E	hunched posture, slightly lethargic, squinting	8	10
13-0796	318 mg/kg-day ^E	rough coat	9	10
13-0796	318 mg/kg-day ^E	bloody bedding in cage	10	10
13-0796	318 mg/kg-day ^E	MK	10	
13-0805	318 mg/kg-day ^E	wet chin after dosing, squinting, prostrate, lethargic	7	7
13-0805	318 mg/kg-day ^E	lethargic, dried red material on front paws, squinting, hair loss around right eye with irritation, hunched posture, rough coat, labored breathing	8	8
13-0805	318 mg/kg-day ^E	MK	8	
13-0806	318 mg/kg-day ^E	squinting, prostrate	8	9
13-0806	318 mg/kg-day ^E	barbering both front paws, slightly lethargic	8	10
13-0806	318 mg/kg-day ^E	dried red material both front paws, hunched posture, rough coat	10	10
13-0806	318 mg/kg-day ^E	not dosed- MK	10	
13-0813	318 mg/kg-day ^E	no abnormalities observed		
13-0814	318 mg/kg-day ^E	no abnormalities observed		
13-0825	318 mg/kg-day ^E	slightly lethargic	3	5
13-0825	318 mg/kg-day ^E	dried red material on front paws, bloody urination	5	5
13-0825	318 mg/kg-day ^E	not dosed- MK	5	
13-0826	318 mg/kg-day ^E	lethargic, squinting	0	3
13-0826	318 mg/kg-day ^E	congested breathing	1	3
13-0826	318 mg/kg-day ^E	hunched posture	2	3
13-0826	318 mg/kg-day ^E	slightly lethargic	5	9
13-0826	318 mg/kg-day ^E	dried red material on left front paw	6	6

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13-0826	318 mg/kg-day ^E	hunched posture, rough coat	6	9
13-0826	318 mg/kg-day ^E	slightly congested breathing	7	7
13-0826	318 mg/kg-day ^E	squinting	7	8
13-0826	318 mg/kg-day ^E	dried red material both front paws, prostrate	8	8
13-0826	318 mg/kg-day ^E	brown perianal staining	8	9
13-0826	318 mg/kg-day ^E	bloody bedding in cage	9	9
13-0826	318 mg/kg-day ^E	not dosed- MK	9	
13-0839	318 mg/kg-day ^E	slightly congested breathing, blood from nose when dosed, prostrate	12	12
13-0839	318 mg/kg-day ^E	slightly lethargic, rough coat, hunched posture	14	14
13-0840	318 mg/kg-day ^E	slightly lethargic	14	14

*Concentration: 3.125 mg/ml^A, 6.25 mg/ml^B, 12.5 mg/ml^C, 25 mg/ml^D, 50 mg/ml^E

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Table D-6
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
Sodium Periodate 14-Day Clinical Observations
Male Rats

Animal No.	Dose Group*	Clinical Sign	Day of First Appearance	Day of Last Appearance
13-0855	Water Control	small abrasion center of back	0	1
13-0856	Water Control	no abnormalities observed		
13-0873	Water Control	no abnormalities observed		
13-0874	Water Control	no abnormalities observed		
13-0879	Water Control	no abnormalities observed		
13-0880	Water Control	no abnormalities observed		
13-0891	Water Control	no abnormalities observed		
13-0892	Water Control	no abnormalities observed		
13-0901	Water Control	no abnormalities observed		
13-0902	Water Control	no abnormalities observed		
13-0861	47 mg/kg-day ^B	no abnormalities observed		
13-0862	47 mg/kg-day ^B	barbering both front paws	7	14
13-0865	47 mg/kg-day ^B	no abnormalities observed		
13-0866	47 mg/kg-day ^B	no abnormalities observed		
13-0869	47 mg/kg-day ^B	no abnormalities observed		
13-0870	47 mg/kg-day ^B	no abnormalities observed		
13-0889	47 mg/kg-day ^B	laceration dorsal right lateral	7	8
13-0889	47 mg/kg-day ^B	scab dorsal right lateral	9	10
13-0889	47 mg/kg-day ^B	hair loss dorsal lateral right	11	12
13-0890	47 mg/kg-day ^B	no abnormalities observed		
13-0911	47 mg/kg-day ^B	no abnormalities observed		
13-0912	47 mg/kg-day ^B	no abnormalities observed		
13-0859	93 mg/kg-day ^C	no abnormalities observed		
13-0860	93 mg/kg-day ^C	no abnormalities observed		
13-0875	93 mg/kg-day ^C	no abnormalities observed		
13-0876	93 mg/kg-day ^C	no abnormalities observed		
13-0881	93 mg/kg-day ^C	small scab left shoulder	13	13
13-0882	93 mg/kg-day ^C	no abnormalities observed		
13-0899	93 mg/kg-day ^C	no abnormalities observed		
13-0900	93 mg/kg-day ^C	no abnormalities observed		
13-0909	93 mg/kg-day ^C	no abnormalities observed		

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13-0910	93 mg/kg-day ^C	no abnormalities observed		
13-0867	182.25 mg/kg-day ^D	no abnormalities observed		
13-0868	182.25 mg/kg-day ^D	no abnormalities observed		
13-0877	182.25 mg/kg-day ^D	prostrate, squinting	11	11
13-0877	182.25 mg/kg-day ^D	slightly lethargic	11	13
13-0877	182.25 mg/kg-day ^D	rough coat	11	14
13-0877	182.25 mg/kg-day ^D	hunched posture	13	14
13-0878	182.25 mg/kg-day ^D	blood coming from nose before dosing	3	3
13-0878	182.25 mg/kg-day ^D	slightly lethargic	5	12
13-0878	182.25 mg/kg-day ^D	hunched posture	5	10
13-0878	182.25 mg/kg-day ^D	diarrhea, brown perianal staining	6	6
13-0878	182.25 mg/kg-day ^D	rough coat	7	13
13-0878	182.25 mg/kg-day ^D	squinting	7	13
13-0878	182.25 mg/kg-day ^D	prostrate	11	13
13-0878	182.25 mg/kg-day ^D	brown perianal staining	12	13
13-0878	182.25 mg/kg-day ^D	lethargic, labored breathing	13	13
13-0878	182.25 mg/kg-day ^D	MK	13	
13-0883	182.25 mg/kg-day ^D	dried red material both front paws and nose	14	14
13-0884	182.25 mg/kg-day ^D	no abnormalities observed		
13-0897	182.25 mg/kg-day ^D	chromodacryorrhea both eyes	4	4
13-0897	182.25 mg/kg-day ^D	slightly lethargic	7	9
13-0897	182.25 mg/kg-day ^D	prostrate	7	8
13-0897	182.25 mg/kg-day ^D	squinting	8	8
13-0897	182.25 mg/kg-day ^D	soft feces	10	10
13-0897	182.25 mg/kg-day ^D	squinting, prostrate	12	12
13-0898	182.25 mg/kg-day ^D	slightly lethargic	9	9
13-0903	182.25 mg/kg-day ^D	soft feces	13	13
13-0904	182.25 mg/kg-day ^D	no abnormalities observed		
13-0857	370 mg/kg-day ^E	dried red material around nose	1	1
13-0857	370 mg/kg-day ^E	chromodacryorrhea left eye	6	6
13-0857	370 mg/kg-day ^E	hunched posture, lethargic, curled front toes, squinting, rough coat, chromodacryorrhea both eyes, dried red material both front paws	7	7
13-0857	370 mg/kg-day ^E	not dosed - MK	7	
13-0858	370 mg/kg-day ^E	slightly lethargic, rough coat	11	12
13-0858	370 mg/kg-day ^E	prostrate, squinting	12	12
13-0858	370 mg/kg-day ^E	MK	12	

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13-0871	370 mg/kg-day ^E	slightly lethargic	3	10
13-0871	370 mg/kg-day ^E	rough coat	9	10
13-0871	370 mg/kg-day ^E	hunched posture, dried red material both front paws	10	10
13-0871	370 mg/kg-day ^E	FD	10	
13-0872	370 mg/kg-day ^E	congested breathing	4	4
13-0872	370 mg/kg-day ^E	slightly lethargic, rough coat, dried red material both front paws	7	7
13-0872	370 mg/kg-day ^E	MK	7	
13-0893	370 mg/kg-day ^E	slightly lethargic, squinting, prostrate	3	3
13-0893	370 mg/kg-day ^E	bleeding laceration on insided of lip	4	4
13-0893	370 mg/kg-day ^E	dark feces in cage	9	9
13-0893	370 mg/kg-day ^E	slightly lethargic	9	10
13-0893	370 mg/kg-day ^E	hunched posture	10	10
13-0893	370 mg/kg-day ^E	chromodacryorrhea left eye, rough coat	10	11
13-0893	370 mg/kg-day ^E	brown perianal staining, dried red material both front paws, lethargic, diarrhea	11	11
13-0893	370 mg/kg-day ^E	not dosed - MK	11	
13-0894	370 mg/kg-day ^E	slightly lethargic	2	2
13-0894	370 mg/kg-day ^E	congested breathing	6	6
13-0894	370 mg/kg-day ^E	dark feces in cage	9	9
13-0894	370 mg/kg-day ^E	slightly lethargic	9	11
13-0894	370 mg/kg-day ^E	rough coat	10	10
13-0894	370 mg/kg-day ^E	prostrate	10	11
13-0894	370 mg/kg-day ^E	squinting, dried red material both front paws	11	11
13-0894	370 mg/kg-day ^E	FD	11	
13-0895	370 mg/kg-day ^E	slightly lethargic	5	8
13-0895	370 mg/kg-day ^E	dark feces, squinting	6	8
13-0895	370 mg/kg-day ^E	hunched posture, rough coat	6	9
13-0895	370 mg/kg-day ^E	dried red material both front paws	7	9
13-0895	370 mg/kg-day ^E	brown perianal staining	8	9
13-0895	370 mg/kg-day ^E	lethargic, squinting, pale mucous membranes	9	9
13-0895	370 mg/kg-day ^E	MK	9	
13-0896	370 mg/kg-day ^E	slightly lethargic	2	2
13-0896	370 mg/kg-day ^E	chromodacryorrhea right eye, labored breathing	3	3
13-0896	370 mg/kg-day ^E	rough coat, hunched posture	3	4

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13-0896	370 mg/kg-day ^E	squinting, slightly lethargic	4	
13-0896	370 mg/kg-day ^E	MK	4	
13-0905	370 mg/kg-day ^E	hunched posture	4	4
13-0905	370 mg/kg-day ^E	rough coat	4	7
13-0905	370 mg/kg-day ^E	slightly lethargic	4	6
13-0905	370 mg/kg-day ^E	vocalized during dosing	6	6
13-0905	370 mg/kg-day ^E	lethargic, dried red material both front paws, ataxia	7	7
13-0905	370 mg/kg-day ^E	not dosed - MK	7	
13-0906	370 mg/kg-day ^E	slightly lethargic	2	2
13-0906	370 mg/kg-day ^E	squinting, lethargic, rough coat, hunched posture, bloody bedding	3	3
13-0906	370 mg/kg-day ^E	MK	3	
13-0863	741 mg/kg-day ^F	slightly lethargic	1	3
13-0863	741 mg/kg-day ^F	prostrate, squinting, lethargic, labored breathing	4	5
13-0863	741 mg/kg-day ^F	rough coat, hunched posture, dried red material both front paws and nose/mouth	5	5
13-0863	741 mg/kg-day ^F	not dosed - MK	5	
13-0864	741 mg/kg-day ^F	slightly lethargic	2	3
13-0864	741 mg/kg-day ^F	brown/yellow perianal staining, dried red material both front paws, squinting, hunched posture	3	4
13-0864	741 mg/kg-day ^F	dried red material around nose, ataxia, blood stained bedding by anus, lethargic, bloody diarrhea, bloody urine	4	4
13-0864	741 mg/kg-day ^F	not dosed - MK	4	
13-0885	741 mg/kg-day ^F	slightly lethargic	1	4
13-0885	741 mg/kg-day ^F	yellow/brown perianal staining, hunched posture, dried red material both front paws, lethargic	4	4
13-0885	741 mg/kg-day ^F	MK	4	
13-0886	741 mg/kg-day ^F	slightly congested breathing prior to first dosing	0	
13-0886	741 mg/kg-day ^F	FD	4	
13-0887	741 mg/kg-day ^F	rough coat, dark yellow urogenital staining, bloody urine, prostrate	4	4
13-0887	741 mg/kg-day ^F	FD	4	
13-0888	741 mg/kg-day ^F	mouth/chin wet after dosing	1	1
13-0888	741 mg/kg-day ^F	slightly lethargic	4	5

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13-0888	741 mg/kg-day ^F	congested breathing, rough coat, hunched posture, prostrate, labored breathing	5	5
13-0888	741 mg/kg-day ^F	MK	5	
13-0907	741 mg/kg-day ^F	slightly lethargic	2	2
13-0907	741 mg/kg-day ^F	brown/yellow perianal staining, hunched posture, slightly lethargic, diarrhea	3	3
13-0907	741 mg/kg-day ^F	FD	4	
13-0908	741 mg/kg-day ^F	congested breathing, red material around nose, slightly lethargic	3	4
13-0908	741 mg/kg-day ^F	rough coat, dried red material around nose/mouth, hunched posture, yellow/brown perianal staining	4	4
13-0908	741 mg/kg-day ^F	not dosed - MK	4	
13-0913	741 mg/kg-day ^F	chromodacryorrhea both eyes	1	1
13-0913	741 mg/kg-day ^F	FD	2	
13-0914	741 mg/kg-day ^F	prostrate, lethargic	3	3
13-0914	741 mg/kg-day ^F	MK	3	

*Concentration: 6.25 mg/ml^B, 12.5 mg/ml^C, 25 mg/ml^D, 50 mg/ml^E, 100 mg/ml^F

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Appendix E

Individual and Summary of Body Mass Data

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Table E-1
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
14-Day Individual Body Mass (grams)
Female Rats

Group	Animal ID	Day 0	Day 1	Day 3	Day 7	Day 13
Control	13-0799	211.7	220	227.7	243.2	258.3
	13-0800	223.5	225.6	225.2	235.2	252.8
	13-0811	207.5	207.8	213.9	222.9	238.8
	13-0812	217.4	225.5	233.5	242.4	255
	13-0815	247.1	250.6	258.9	275	300.4
	13-0816	239.2	234.3	238.4	239.2	263.6
	13-0821	212.5	210.5	219.3	214.5	243.7
	13-0822	213.9	218.9	217.7	230.2	253.6
	13-0831	231.3	228	244.9	249.5	260.7
	13-0832	239.3	244.6	247	249.4	263.6
	Mean	224.3	226.6	232.7	240.2	259.1
	SD	13.95	13.66	14.58	16.61	16.62
20 mg/kg	13-0823	205.4	217.5	222.1	229.2	238.7
	13-0824	209.9	212.9	220.8	223.7	237.3
	13-0833	210.2	212.5	209	210.4	227.8
	13-0834	220.8	219.8	224.7	230.8	242.4
	13-0835	212.7	214.2	217.3	227.7	236.9
	13-0836	241.7	247.7	241.6	252	272.6
	13-0841	228.9	231	234	238.9	248
	13-0842	236.5	234.1	243.4	248.6	260.6
	13-0843	232.7	235.4	244.4	245.3	251
	13-0844	227.5	232.5	232.3	232.3	253.6
	Mean	222.6	225.8	229.0	233.9	246.9
	SD	12.63	12.00	12.06	12.59	13.15
40 mg/kg	13-0807	237.8	243.8	246.7	257.4	256.1
	13-0808	209.6	220.6	226.5	235.6	253.4
	13-0817	218.7	223.5	217	222.8	243.3
	13-0818	226.7	217.4	231.9	245.6	253.6
	13-0819	244.7	246.7	250.5	259.7	269.4
	13-0820	247.5	257.1	263	272.8	285.9
	13-0845	239.1	241.8	241.9	247.7	265.3
	13-0846	204.8	207.4	207.2	207.3	225.7
	13-0847	238.9	239.5	242.5	252	258.6
	13-0848	209.8	218.9	226.2	235.3	239.5
	Mean	227.8	231.7	235.3	243.6	255.1

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	SD	15.96	16.09	16.73	19.08	16.74
80 mg/kg	13-0797	218.7	231	229.9	232.5	241.2
	13-0798	212.1	218.1	219.1	225.4	236.5
	13-0809	215.9	217	213.3	221.8	247.4
	13-0810	220.5	214.3	225.2	231.8	230.4
	13-0827	226.8	231.3	236.4	247.4	265.6
	13-0828	212.8	223	227.8	228.3	240.5
	13-0851	232	233.6	235.3	233.7	239.2
	13-0852	234.1	238	234.1	247.3	264.9
	13-0853	237.8	233.1	238.2	243.5	253
	13-0854	209.4	210.9	206	209.6	230.4
	Mean	222.0	225.0	226.5	232.1	244.9
	SD	10.06	9.51	10.72	11.88	12.72
159 mg/kg	13-0801	217.4	220.2	212.6	220.5	233.2
	13-0802	234.9	245.4	246.1	259.7	250
	13-0803	208.2	207.7	200.9	202.9	219.2
	13-0804	227.7	228	234	240.1	243.5
	13-0829	206	207.2	213.4	214.1	210
	13-0830	242.5	241.6	248.1	251.5	257.3
	13-0837	255.4	252.3	267.2	276.8	283.7
	13-0838	243.8	252.2	252.7	263.2	274.9
	13-0849	223.9	222	229.7	233.7	236.2
	13-0850	229.4	231.2	233.2	238.6	242.2
	Mean	228.9	230.8	233.8	240.1	245.0
	SD	15.84	16.79	20.53	23.29	22.82
318 mg/kg	13-0795	226	226.7	204.7	224.4	231.5
	13-0796	236	231	233.2	233.5	
	13-0805	220.3	228.9	222.4	217	
	13-0806	230	229.5	232.2	238.9	
	13-0813	223.2	230.9	225.9	219.2	236.7
	13-0814	210.9	215.9	214	217.2	212.7
	13-0825	202	203.7	191.7		
	13-0826	224.8	218.2	214.6	211.8	
	13-0839	228.1	238.6	235.5	240.2	244.1
	13-0840	213.7	216.5	212.7	219.1	218.5
	Mean	221.5	224.0	218.7	224.6	228.7*
	SD	10.08	10.21	13.91	10.39	12.93

*Significantly different from control

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Table E-2
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Body Mass (grams)						
Male Rats						
Group	Animal ID	Day 0	Day 1	Day 3	Day 7	Day 13
Control	13-0855	288.2	298	310	330.8	369.1
	13-0856	277.2	280.5	292.7	315.5	347.3
	13-0873	303.5	311.1	324.8	352.4	398.8
	13-0874	289.5	292.8	307.3	331.9	365.3
	13-0879	270.4	274.7	288.8	307.6	342.7
	13-0880	299.2	303.2	318.7	350.2	393.7
	13-0891	296.4	299.4	315.1	342.9	382.8
	13-0892	296.6	298.9	319.2	342.9	380
	13-0901	325.4	339.2	356.4	401	446.6
	13-0902	275.1	281.3	289.5	307.8	329.4
	Mean	292.2	297.9	312.3	338.3	375.6
	SD	16.10	18.42	20.23	27.50	33.57
47 mg/kg	13-0861	275.6	279.1	294	324	364.9
	13-0862	284.9	289.8	301.8	333.3	374.8
	13-0865	265.9	268.5	278.2	298.6	322
	13-0866	303.1	314.6	325.4	352.1	387.9
	13-0869	272.1	277	288.5	307.1	335.7
	13-0870	280.1	284.4	290.8	307.7	338.3
	13-0889	313.9	315.5	329.2	353.7	384.7
	13-0890	306.1	309.4	318.3	336.7	366.5
	13-0911	303.9	315.4	323.1	348.6	382.6
	13-0912	301.2	308.1	315	342.4	379.2
	Mean	290.7	296.2	306.4	330.4	363.7
	SD	16.83	18.27	17.98	20.13	23.39
93 mg/kg	13-0859	273.5	283.4	293.1	308.7	335.6
	13-0860	256.6	261.4	270.5	292.5	319.6
	13-0875	275.6	277.1	291.2	306.8	338.3
	13-0876	276.2	287.2	289.5	312.2	333.2
	13-0881	290.7	302.5	302.8	318.6	347.5
	13-0882	284.2	293.9	302.5	331.9	358.3
	13-0899	311.3	315.8	332.6	359.1	387.6
	13-0900	285.6	290.5	296.2	320.6	346.9
	13-0909	317.5	316.2	325.2	353.7	383.6
	13-0910	328.8	339.3	350.4	381.3	414.5
	Mean	290.0	296.7	305.4	328.5	356.5

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	SD	22.50	22.45	23.76	27.80	29.65
185 mg/kg	13-0867	280.7	284	286.7	320.1	329.1
	13-0868	282.2	287.5	304.1	328.1	360.5
	13-0877	272.8	272.8	280	286.7	287.2
	13-0878	263.8	258.3	239.4	231.7	222.7
	13-0883	285.6	287.6	299.7	328.1	318.9
	13-0884	282.8	288	296.6	316.4	336.8
	13-0897	292.8	297.3	308.6	316.5	337.8
	13-0898	305.8	308.4	317.2	333.2	367.5
	13-0903	283.4	284.8	286.8	280.4	302.5
	13-0904	302.7	306.9	318.3	323.3	351.6
	Mean	285.3	287.6	293.7	306.5	321.5*
	SD	12.64	14.90	23.04	31.59	42.70
370 mg/kg	13-0857	281.1	279.8	291.2	250.7	
	13-0858	266.5	264.3	264	275.5	
	13-0871	277.6	285.1	276.3	266.5	
	13-0872	294.3	302.3	298.3	272.2	
	13-0893	261.4	259	265.2	269	
	13-0894	289.7	293.5	275.1	278.2	
	13-0895	321.2	324.1	329.3	310.4	
	13-0896	306.9	305.1	281.3		
	13-0905	301.1	302.5	301.1	262.1	
	13-0906	275.8	277	266.7		
	Mean	287.6	289.3	284.9*	273.1*	
	SD	18.70	20.07	20.53	17.35	
741 mg/kg	13-0863	271.2	274.3	265.7		
	13-0864	260.2	249.6	229.2		
	13-0885	281.1	288.6	269.1		
	13-0886	268.9	272.9	256.2		
	13-0887	283.2	285.1	268.1		
	13-0888	295.5	292.1	279.4		
	13-0907	285.2	285.7	269.4		
	13-0908	288.6	287.8	274.4		
	13-0913	304	289.9			
	13-0914	277.5	281.6	260.5		
	Mean	281.5	280.8	263.5*		
	SD	12.93	12.66	14.59		

*Significantly different from control

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Appendix F

Individual and Summary of Body Mass Gain Data

Toxicity Report No. S.0015656-13, July–August 2013

Table F-1
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
14-Day Individual Body Mass Gain (grams)
Female Rats

Group	Animal ID	Day 0-1	Day 1-3	Day 3-7	Day 7-13	Net
Control	13-0799	8.3	7.7	15.5	15.1	46.6
	13-0800	2.1	-0.4	10	17.6	29.3
	13-0811	0.3	6.1	9	15.9	31.3
	13-0812	8.1	8	8.9	12.6	37.6
	13-0815	3.5	8.3	16.1	25.4	53.3
	13-0816	-4.9	4.1	0.8	24.4	24.4
	13-0821	-2	8.8	-4.8	29.2	31.2
	13-0822	5	-1.2	12.5	23.4	39.7
	13-0831	-3.3	16.9	4.6	11.2	29.4
	13-0832	5.3	2.4	2.4	14.2	24.3
	Mean	2.2	6.1	7.5	18.9	34.7
	SD	4.63	5.25	6.70	6.19	9.52
20 mg/kg	13-0823	12.1	4.6	7.1	9.5	33.3
	13-0824	3	7.9	2.9	13.6	27.4
	13-0833	2.3	-3.5	1.4	17.4	17.6
	13-0834	-1	4.9	6.1	11.6	21.6
	13-0835	1.5	3.1	10.4	9.2	24.2
	13-0836	6	-6.1	10.4	20.6	30.9
	13-0841	2.1	3	4.9	9.1	19.1
	13-0842	-2.4	9.3	5.2	12	24.1
	13-0843	2.7	9	0.9	5.7	18.3
	13-0844	5	-0.2	0	21.3	26.1
	Mean	3.1	3.2	4.9	13.0	24.3
	SD	4.01	5.17	3.70	5.21	5.30
40 mg/kg	13-0807	6	2.9	10.7	-1.3	18.3
	13-0808	11	5.9	9.1	17.8	43.8
	13-0817	4.8	-6.5	5.8	20.5	24.6
	13-0818	-9.3	14.5	13.7	8	26.9
	13-0819	2	3.8	9.2	9.7	24.7
	13-0820	9.6	5.9	9.8	13.1	38.4
	13-0845	2.7	0.1	5.8	17.6	26.2
	13-0846	2.6	-0.2	0.1	18.4	20.9
	13-0847	0.6	3	9.5	6.6	19.7
	13-0848	9.1	7.3	9.1	4.2	29.7
	Mean	3.9	3.7	8.3	11.5	27.3

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	SD	5.84	5.50	3.66	7.19	8.14
80 mg/kg	13-0797	12.3	-1.1	2.6	8.7	22.5
	13-0798	6	1	6.3	11.1	24.4
	13-0809	1.1	-3.7	8.5	25.6	31.5
	13-0810	-6.2	10.9	6.6	-1.4	9.9
	13-0827	4.5	5.1	11	18.2	38.8
	13-0828	10.2	4.8	0.5	12.2	27.7
	13-0851	1.6	1.7	-1.6	5.5	7.2
	13-0852	3.9	-3.9	13.2	17.6	30.8
	13-0853	-4.7	5.1	5.3	9.5	15.2
	13-0854	1.5	-4.9	3.6	20.8	21
	Mean	3.0	1.5	5.6	12.8	22.9*
	SD	5.79	5.05	4.57	7.93	9.96
159 mg/kg	13-0801	2.8	-7.6	7.9	12.7	15.8
	13-0802	10.5	0.7	13.6	-9.7	15.1
	13-0803	-0.5	-6.8	2	16.3	11
	13-0804	0.3	6	6.1	3.4	15.8
	13-0829	1.2	6.2	0.7	-4.1	4
	13-0830	-0.9	6.5	3.4	5.8	14.8
	13-0837	-3.1	14.9	9.6	6.9	28.3
	13-0838	8.4	0.5	10.5	11.7	31.1
	13-0849	-1.9	7.7	4	2.5	12.3
	13-0850	1.8	2	5.4	3.6	12.8
	Mean	1.9	3.0	6.3	4.9*	16.1*
	SD	4.39	6.80	4.07	7.79	7.99
318 mg/kg	13-0795	0.7	-22	19.7	7.1	5.5
	13-0796	-5	2.2	0.3		
	13-0805	8.6	-6.5	-5.4		
	13-0806	-0.5	2.7	6.7		
	13-0813	7.7	-5	-6.7	17.5	13.5
	13-0814	5	-1.9	3.2	-4.5	1.8
	13-0825	1.7	-12			
	13-0826	-6.6	-3.6	-2.8		
	13-0839	10.5	-3.1	4.7	3.9	16
	13-0840	2.8	-3.8	6.4	-0.6	4.8
	Mean	2.5	-5.3*	2.9	4.7*	8.3*
	SD	5.64	7.20	8.00	8.41	6.10

*Significantly different from control

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Table F-2
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
14-Day Individual Body Mass Gain (grams)
Male Rats

Group	Animal ID	Day 0-1	Day 1-3	Day 3-7	Day 7-13	Net
Control	13-0855	9.8	12	20.8	38.3	80.9
	13-0856	3.3	12.2	22.8	31.8	70.1
	13-0873	7.6	13.7	27.6	46.4	95.3
	13-0874	3.3	14.5	24.6	33.4	75.8
	13-0879	4.3	14.1	18.8	35.1	72.3
	13-0880	4	15.5	31.5	43.5	94.5
	13-0891	3	15.7	27.8	39.9	86.4
	13-0892	2.3	20.3	23.7	37.1	83.4
	13-0901	13.8	17.2	44.6	45.6	121.2
	13-0902	6.2	8.2	18.3	21.6	54.3
	Mean	5.8	14.3	26.1	37.3	83.4
	SD	3.67	3.25	7.73	7.41	17.99
47 mg/kg	13-0861	3.5	14.9	30	40.9	89.3
	13-0862	4.9	12	31.5	41.5	89.9
	13-0865	2.6	9.7	20.4	23.4	56.1
	13-0866	11.5	10.8	26.7	35.8	84.8
	13-0869	4.9	11.5	18.6	28.6	63.6
	13-0870	4.3	6.4	16.9	30.6	58.2
	13-0889	1.6	13.7	24.5	31	70.8
	13-0890	3.3	8.9	18.4	29.8	60.4
	13-0911	11.5	7.7	25.5	34	78.7
	13-0912	6.9	6.9	27.4	36.8	78
	Mean	5.5	10.3	24.0	33.2	73.0
	SD	3.47	2.85	5.14	5.67	12.93
93 mg/kg	13-0859	9.9	9.7	15.6	26.9	62.1
	13-0860	4.8	9.1	22	27.1	63
	13-0875	1.5	14.1	15.6	31.5	62.7
	13-0876	11	2.3	22.7	21	57
	13-0881	11.8	0.3	15.8	28.9	56.8
	13-0882	9.7	8.6	29.4	26.4	74.1
	13-0899	4.5	16.8	26.5	28.5	76.3
	13-0900	4.9	5.7	24.4	26.3	61.3
	13-0909	-1.3	9	28.5	29.9	66.1
	13-0910	10.5	11.1	30.9	33.2	85.7
	Mean	6.7	8.7	23.1	28.0	66.5

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	SD	4.48	4.97	5.87	3.34	9.31
185 mg/kg	13-0867	3.3	2.7	33.4	9	48.4
	13-0868	5.3	16.6	24	32.4	78.3
	13-0877	0	6.7	7.2	0.5	14.4
	13-0878	-5.5	-18.9	-7.7	-9	-41.1
	13-0883	2	12.1	28.4	-9.2	33.3
	13-0884	5.2	8.6	19.8	20.4	54
	13-0897	4.5	11.3	7.9	21.3	45
	13-0898	2.6	8.8	16	34.3	61.7
	13-0903	1.4	2	-6.4	22.1	19.1
	13-0904	4.2	11.4	5	28.3	48.9
	Mean	2.3	6.1	12.8	15.0*	36.2*
	SD	3.23	9.82	13.97	16.26	33.13
370 mg/kg	13-0857	-1.3	11.4	-40.5		
	13-0858	-2.2	-0.3	11.5		
	13-0871	7.5	-8.8	-9.8		
	13-0872	8	-4	-26.1		
	13-0893	-2.4	6.2	3.8		
	13-0894	3.8	-18.4	3.1		
	13-0895	2.9	5.2	-18.9		
	13-0896	-1.8	-23.8			
	13-0905	1.4	-1.4	-39		
	13-0906	1.2	-10.3			
	Mean	1.7	-4.4*	-14.5*		
	SD	3.84	11.09	19.90		
741 mg/kg	13-0863	3.1	-8.6			
	13-0864	-10.6	-20.4			
	13-0885	7.5	-19.5			
	13-0886	4	-16.7			
	13-0887	1.9	-17			
	13-0888	-3.4	-12.7			
	13-0907	0.5	-16.3			
	13-0908	-0.8	-13.4			
	13-0913	-14.1				
	13-0914	4.1	-21.1			
	Mean	-0.8*	-16.2*			
	SD	6.83	4.05			

*Significantly different from control

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Table F-3
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
14-Day Individual Percent Body Mass Gain
Female Rats

Group	Animal ID	Day 1	Day 3	Day 7	Day 13
Control	13-0799	3.92	7.56	14.88	22.01
	13-0800	0.94	0.76	5.23	13.11
	13-0811	0.14	3.08	7.42	15.08
	13-0812	3.73	7.41	11.50	17.30
	13-0815	1.42	4.78	11.29	21.57
	13-0816	-2.05	-0.33	0.00	10.20
	13-0821	-0.94	3.20	0.94	14.68
	13-0822	2.34	1.78	7.62	18.56
	13-0831	-1.43	5.88	7.87	12.71
	13-0832	2.21	3.22	4.22	10.15
	Mean	1.03	3.73	7.10	15.54
	SD	2.08	2.67	4.70	4.25
20 mg/kg	13-0823	5.89	8.13	11.59	16.21
	13-0824	1.43	5.19	6.57	13.05
	13-0833	1.09	-0.57	0.10	8.37
	13-0834	-0.45	1.77	4.53	9.78
	13-0835	0.71	2.16	7.05	11.38
	13-0836	2.48	-0.04	4.26	12.78
	13-0841	0.92	2.23	4.37	8.34
	13-0842	-1.01	2.92	5.12	10.19
	13-0843	1.16	5.03	5.41	7.86
	13-0844	2.20	2.11	2.11	11.47
	Mean	1.44	2.89	5.11	10.95
	SD	1.89	2.60	3.05	2.60
40 mg/kg	13-0807	2.52	3.74	8.24	7.70
	13-0808	5.25	8.06	12.40	20.90
	13-0817	2.19	-0.78	1.87	11.25
	13-0818	-4.10	2.29	8.34	11.87
	13-0819	0.82	2.37	6.13	10.09
	13-0820	3.88	6.26	10.22	15.52
	13-0845	1.13	1.17	3.60	10.96
	13-0846	1.27	1.17	1.22	10.21
	13-0847	0.25	1.51	5.48	8.25
	13-0848	4.34	7.82	12.15	14.16
	Mean	1.75	3.36	6.97	12.09

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	SD	2.63	3.03	4.00	3.90
80 mg/kg	13-0797	5.62	5.12	6.31	10.29
	13-0798	2.83	3.30	6.27	11.50
	13-0809	0.51	-1.20	2.73	14.59
	13-0810	-2.81	2.13	5.12	4.49
	13-0827	1.98	4.23	9.08	17.11
	13-0828	4.79	7.05	7.28	13.02
	13-0851	0.69	1.42	0.73	3.10
	13-0852	1.67	0.00	5.64	13.16
	13-0853	-1.98	0.17	2.40	6.39
	13-0854	0.72	-1.62	0.10	10.03
	Mean	1.40	2.06	4.57	10.37*
	SD	2.64	2.85	2.94	4.50
159 mg/kg	13-0801	1.29	-2.21	1.43	7.27
	13-0802	4.47	4.77	10.56	6.43
	13-0803	-0.24	-3.51	-2.55	5.28
	13-0804	0.13	2.77	5.45	6.94
	13-0829	0.58	3.59	3.93	1.94
	13-0830	-0.37	2.31	3.71	6.10
	13-0837	-1.21	4.62	8.38	11.08
	13-0838	3.45	3.65	7.96	12.76
	13-0849	-0.85	2.59	4.38	5.49
	13-0850	0.78	1.66	4.01	5.58
	Mean	0.80	2.02	4.73	6.89*
	SD	1.84	2.77	3.72	3.05
318 mg/kg	13-0795	0.31	-9.42	-0.71	2.43
	13-0796	-2.12	-1.19	-1.06	
	13-0805	3.90	0.95	-1.50	
	13-0806	-0.22	0.96	3.87	
	13-0813	3.45	1.21	-1.79	6.05
	13-0814	2.37	1.47	2.99	0.85
	13-0825	0.84	-5.10		
	13-0826	-2.94	-4.54	-5.78	
	13-0839	4.60	3.24	5.30	7.01
	13-0840	1.31	-0.47	2.53	2.25
	Mean	1.15	-1.29*	0.43*	3.72*
	SD	2.50	3.89	3.49	2.66

*Significantly different from control

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Table F-4
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
14-Day Individual Percent Body Mass Gain
Male Rats

Group	Animal ID	Day1	Day 3	Day 7	Day 13
Control	13-0855	3.40	7.56	14.78	28.07
	13-0856	1.19	5.59	13.82	25.29
	13-0873	2.50	7.02	16.11	31.40
	13-0874	1.14	6.15	14.65	26.18
	13-0879	1.59	6.80	13.76	26.74
	13-0880	1.34	6.52	17.05	31.58
	13-0891	1.01	6.31	15.69	29.15
	13-0892	0.78	7.62	15.61	28.12
	13-0901	4.24	9.53	23.23	37.25
	13-0902	2.25	5.23	11.89	19.74
	Mean	1.94	6.83	15.66	28.35
	SD	1.14	1.22	3.03	4.60
47 mg/kg	13-0861	1.27	6.68	17.56	32.40
	13-0862	1.72	5.93	16.99	31.55
	13-0865	0.98	4.63	12.30	21.10
	13-0866	3.79	7.36	16.17	27.98
	13-0869	1.80	6.03	12.86	23.37
	13-0870	1.54	3.82	9.85	20.78
	13-0889	0.51	4.87	12.68	22.55
	13-0890	1.08	3.99	10.00	19.73
	13-0911	3.78	6.32	14.71	25.90
	13-0912	2.29	4.58	13.68	25.90
	Mean	1.88	5.42	13.68	25.13
	SD	1.12	1.20	2.69	4.44
93 mg/kg	13-0859	3.62	7.17	12.87	22.71
	13-0860	1.87	5.42	13.99	24.55
	13-0875	0.54	5.66	11.32	22.75
	13-0876	3.98	4.82	13.03	20.64
	13-0881	4.06	4.16	9.60	19.54
	13-0882	3.41	6.44	16.78	26.07
	13-0899	1.45	6.84	15.35	24.51
	13-0900	1.72	3.71	12.25	21.46
	13-0909	-0.41	2.43	11.40	20.82
	13-0910	3.19	6.57	15.97	26.06
	Mean	2.34	5.32	13.26	22.91

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	SD	1.54	1.54	2.27	2.32
185 mg/kg	13-0867	1.18	2.14	14.04	17.24
	13-0868	1.88	7.76	16.27	27.75
	13-0877	0.00	2.46	5.10	5.28
	13-0878	-2.08	-9.25	-12.17	-15.58
	13-0883	0.70	4.94	14.88	11.66
	13-0884	1.84	4.88	11.88	19.09
	13-0897	1.54	5.40	8.09	15.37
	13-0898	0.85	3.73	8.96	20.18
	13-0903	0.49	1.20	-1.06	6.74
	13-0904	1.39	5.15	6.81	16.15
	Mean	0.78	2.84*	7.28*	12.39*
	SD	1.17	4.65	8.57	11.80
370 mg/kg	13-0857	-0.46	3.59	-10.81	
	13-0858	-0.83	-0.94	3.38	
	13-0871	2.70	-0.47	-4.00	
	13-0872	2.72	1.36	-7.51	
	13-0893	-0.92	1.45	2.91	
	13-0894	1.31	-5.04	-3.97	
	13-0895	0.90	2.52	-3.36	
	13-0896	-0.59	-8.34		
	13-0905	0.46	0.00	-12.95	
	13-0906	0.44	-3.30		
	Mean	0.57	-0.92*	-4.54*	
	SD	1.35	3.68	5.84	
741 mg/kg	13-0863	1.14	-2.03		
	13-0864	-4.07	-11.91		
	13-0885	2.67	-4.27		
	13-0886	1.49	-4.72		
	13-0887	0.67	-5.33		
	13-0888	-1.15	-5.45		
	13-0907	0.18	-5.54		
	13-0908	-0.28	-4.92		
	13-0913	-4.64			
	13-0914	1.48	-6.13		
	Mean	-0.25*	-5.59*		
	SD	2.41	2.65		

*Significantly different from control

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Appendix G

Individual and Summary of Food Consumption Data

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Table G-1
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
14-Day Food Consumption (grams/day)
Female Rats

Group	Animal ID	Days 0-1/day	Days 1-3/day	Days 3-7/day	Days 7-13/day	Total/day
Control	13-0799/00	38.0	39.3	39.2	38.7	38.9
	13-0811/12	35.5	37.7	35.2	36.9	36.4
	13-0815/16	43.6	40.4	43.6	46.5	44.5
	13-0821/22	34.5	34.9	34.3	38.7	36.5
	13-0831/32	40.0	42.1	35.7	39.0	38.5
	Mean	38.3	38.9	37.6	40.0	38.9
	SD	3.65	2.75	3.83	3.76	3.29
20 mg/kg	13-0823/24	38.7	38.7	34.1	35.7	35.9
	13-0833/34	32.7	33.7	34.4	33.8	33.9
	13-0835/36	38.1	33.4	36.5	37.8	36.8
	13-0841/42	39.6	37.6	39.0	39.3	38.9
	13-0843/44	41.4	41.4	34.5	36.6	37.1
	Mean	38.1	36.9	35.7	36.6	36.5
	SD	3.27	3.41	2.08	2.09	1.85
40 mg/kg	13-0807/08	37.4	38.0	37.3	35.7	36.6
	13-0817/18	37.3	35.8	37.1	39.6	38.1
	13-0819/20	41.7	44.4	42.7	42.2	42.6
	13-0845/46	41.7	36.6	36.9	40.2	38.8
	13-0847/48	37.4	37.4	38.2	36.1	37.0
	Mean	39.1	38.4	38.4	38.8	38.6
	SD	2.37	3.42	2.43	2.81	2.40
80 mg/kg	13-0797/98	39.0	36.9	34.8	33.9	35.0
	13-0809/10	32.7	35.4	34.7	36.2	35.4
	13-0827/28	36.2	38.9	35.9	38.2	37.5
	13-0851/52	39.2	35.5	36.2	38.8	37.5
	13-0853/54	31.6	34.9	32.3	36.4	34.5
	Mean	35.7	36.3	34.8	36.7	36.0
	SD	3.51	1.63	1.52	1.94	1.41
159 mg/kg	13-0801/02	38.9	34.9	34.0	30.0	32.7
	13-0803/04	35.7	30.7	33.0	33.8	33.2
	13-0829/30	31.9	37.1	33.4	29.7	32.1
	13-0837/38	40.5	43.5	42.5	42.5	42.5

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	13-0849/50	28.3	35.4	36.7	35.6	35.4
	Mean	35.1	36.3	35.9	34.3	35.2
	SD	5.01	4.65	3.98	5.22	4.28
318 mg/kg*	13-0795/96	28.1	24.9	27.8		14.5
	13-0805/06	36.3	33.4	28.2		16.6
	13-0813/14	31.3	29.2	25.4	30.4	28.7
	13-0825/26	21.8	20.7			4.9
	13-0839/40	30.5	32.3	34.8	28.9	31.4
	Mean	29.6	28.1	29.1	29.6	19.2*
	SD	5.28	5.32	4.03	1.05	10.88

*Significantly different from control

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Table G-2
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
14-Day Paired Food Consumption Per Day (grams)
Male Rats

Group	Animal ID	Days 0-1/day	Days 1-3/day	Days 3-7/day	Days 7-13/day	Total/day
Control	13-0855/56	48.5	50.0	49.2	51.8	50.4
	13-0873/74	49.4	53.2	54.6	56.9	55.0
	13-0879/80	46.3	47.2	48.6	50.6	49.1
	13-0891/92	49.9	55.5	54.3	56.3	55.1
	13-0901/02	55.7	55.1	57.2	55.7	56.1
	Mean	50.0	52.2	52.8	54.2	53.1
	SD	3.49	3.54	3.71	2.89	3.13
47 mg/kg	13-0861/62	46.7	49.1	52.3	55.9	53.0
	13-0865/66	51.4	51.9	53.2	52.4	52.5
	13-0869/70	42.2	44.3	43.5	45.0	44.2
	13-0889/90	45.1	49.0	48.3	47.1	47.6
	13-0911/12	54.2	50.1	54.3	55.1	54.0
	Mean	47.9	48.8	50.3	51.1	50.2
	SD	4.84	2.79	4.43	4.86	4.20
93 mg/kg	13-0859/60	45.0	44.7	43.8	45.2	44.6
	13-0875/76	41.6	47.8	48.1	47.6	47.3
	13-0881/82	46.4	46.2	47.1	46.5	46.6
	13-0899/00	49.3	51.0	52.7	50.7	51.3
	13-0909/10	53.1	54.0	57.0	55.8	55.7
	Mean	47.1	48.7	49.8	49.1	49.1
	SD	4.36	3.77	5.17	4.24	4.39
185 mg/kg*	13-0867/68	46.8	46.7	49.8	44.2	46.5
	13-0877/78	28.1	24.6	25.3	19.8	22.8
	13-0883/84	37.4	41.0	44.6	35.8	39.4
	13-0897/98	48.4	47.4	46.7	44.4	45.9
	13-0903/04	42.9	44.6	37.8	44.1	42.1
	Mean	40.7	40.9	40.8	37.6	39.4*
	SD	8.23	9.45	9.76	10.65	9.68
370 mg/kg	13-0857/58	35.1	35.3	30.8		32.7
	13-0871/72	33.0	34.0	25.3		28.9
	13-0893/94	32.3	27.6	30.3		29.8
	13-0895/96	36.2	32.9			34.0

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	13-0905/06	33.1	23.6		26.7
	Mean	33.9	30.6	28.8	30.4*
	SD	1.64	4.92	3.06	2.92
741 mg/kg	13-0863/64	23.0	15.8		18.2
	13-0885/86	33.5	26.2		28.6
	13-0887/88	25.4	17.8		20.3
	13-0907/08	30.6	24.1		26.3
	13-0913/14	26.6			8.9
	Mean	27.8	21.0		20.5*
	SD	4.20	4.98		7.75

*Significantly different from control

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Table G-3
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
14-Day Food Consumption (grams per day per gram rat)
Female Rats

Group	Animal ID	Days 0-1 (grams per day per gram rat)	Days 1-3 (grams per day per gram rat)	Days 3-7 (grams per day per gram rat)	Days 7-13 (grams per day per gram rat)	Total (grams per day per gram rat)
Control	13-0799/00	0.085	0.087	0.082	0.076	0.076
	13-0811/12	0.082	0.084	0.076	0.075	0.074
	13-0815/16	0.090	0.081	0.085	0.083	0.079
	13-0821/22	0.080	0.080	0.077	0.078	0.073
	13-0831/32	0.085	0.086	0.072	0.074	0.073
	Mean	0.0844	0.0835	0.0782	0.0770	0.0751
	SD	0.00367	0.00291	0.00521	0.00336	0.00239
20 mg/kg	13-0823/24	0.090	0.087	0.075	0.075	0.075
	13-0833/34	0.076	0.078	0.078	0.072	0.072
	13-0835/36	0.082	0.073	0.076	0.074	0.072
	13-0841/42	0.085	0.079	0.080	0.077	0.077
	13-0843/44	0.088	0.087	0.072	0.073	0.073
	Mean	0.0843	0.0806	0.0763	0.0742	0.0739
	SD	0.00566	0.00629	0.00293	0.00212	0.00200
40 mg/kg	13-0807/08	0.081	0.080	0.076	0.070	0.072
	13-0817/18	0.085	0.080	0.079	0.080	0.077
	13-0819/20	0.083	0.086	0.080	0.076	0.077
	13-0845/46	0.093	0.081	0.081	0.082	0.079
	13-0847/48	0.082	0.080	0.078	0.073	0.074
	Mean	0.0845	0.0815	0.0788	0.0760	0.0757
	SD	0.00491	0.00281	0.00213	0.00495	0.00268
80 mg/kg	13-0797/98	0.087	0.082	0.076	0.071	0.073
	13-0809/10	0.076	0.081	0.077	0.076	0.074
	13-0827/28	0.080	0.084	0.076	0.076	0.074
	13-0851/52	0.083	0.076	0.075	0.077	0.074
	13-0853/54	0.071	0.078	0.071	0.075	0.071
	Mean	0.0793	0.0802	0.0749	0.0749	0.0735
	SD	0.00612	0.00321	0.00206	0.00232	0.00118
159 mg/kg*	13-0801/02	0.084	0.076	0.071	0.062	0.068
	13-0803/04	0.082	0.070	0.074	0.073	0.072
	13-0829/30	0.071	0.080	0.072	0.063	0.069

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	13-0837/38	0.080	0.084	0.079	0.076	0.076
	13-0849/50	0.062	0.076	0.078	0.074	0.074
	Mean	0.0759	0.0774	0.0747	0.0698	0.0716
	SD	0.00892	0.00492	0.00356	0.00654	0.00353
318 mg/kg*	13-0795/96	0.061	0.057	0.061		0.063
	13-0805/06	0.079	0.073	0.062		
	13-0813/14	0.070	0.066	0.058	0.068	0.064
	13-0825/26	0.052	0.051			
	13-0839/40	0.067	0.072	0.076	0.062	0.068
	Mean	0.0659	0.0639	0.0641	0.0650	0.0649*
	SD	0.01022	0.00985	0.00792	0.00363	0.00263

***Significantly different from control**

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Table G-4
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
14-Day Food Consumption (grams per day per gram rat)
Male Rats

Group	Animal ID	Days 0-1 (grams per day per gram rat)	Days 1-3 (grams per day per gram rat)	Days 3-7 (grams per day per gram rat)	Days 7-13 (grams per day per gram rat)	Total (grams per day per gram rat)
Control	13-0855/56	0.084	0.083	0.076	0.072	0.070
	13-0873/74	0.082	0.084	0.080	0.075	0.072
	13-0879/80	0.080	0.078	0.074	0.069	0.067
	13-0891/92	0.083	0.087	0.079	0.074	0.072
	13-0901/02	0.090	0.085	0.081	0.072	0.072
	Mean	0.0838	0.0835	0.0779	0.0722	0.0707
	SD	0.00365	0.00366	0.00281	0.00228	0.00237
47 mg/kg	13-0861/62	0.082	0.082	0.079	0.076	0.072
	13-0865/66	0.088	0.086	0.082	0.074	0.074
	13-0869/70	0.075	0.076	0.071	0.067	0.066
	13-0889/90	0.072	0.076	0.070	0.063	0.063
	13-0911/12	0.087	0.078	0.079	0.072	0.071
	Mean	0.0809	0.0797	0.0761	0.0702	0.0691
	SD	0.00706	0.00431	0.00539	0.00537	0.00443
93 mg/kg	13-0859/60	0.083	0.079	0.073	0.069	0.068
	13-0875/76	0.074	0.082	0.078	0.071	0.070
	13-0881/82	0.078	0.076	0.072	0.066	0.066
	13-0899/00	0.081	0.081	0.078	0.069	0.070
	13-0909/10	0.081	0.080	0.078	0.070	0.070
	Mean	0.0793	0.0797	0.0756	0.0689	0.0688
	SD	0.00358	0.00228	0.00274	0.00186	0.00177
185 mg/kg*	13-0867/68	0.082	0.079	0.077	0.064	0.067
	13-0877/78	0.053	0.047	0.049	0.039	0.045
	13-0883/84	0.065	0.069	0.069	0.055	0.060
	13-0897/98	0.080	0.076	0.072	0.063	0.065
	13-0903/04	0.073	0.074	0.063	0.067	0.064
	Mean	0.0704	0.0689	0.0658	0.0575	0.0604*
	SD	0.01186	0.01265	0.01086	0.01152	0.00910
370 mg/kg	13-0857/58	0.065	0.063	0.059		
	13-0871/72	0.056	0.059	0.047		
	13-0893/94	0.058	0.051	0.055		

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	13-0895/96	0.058	0.054	0.000
	13-0905/06	0.057	0.041	0.000
<hr/>				
	Mean	0.0588	0.0538	0.0322
	SD	0.00332	0.00839	0.02967
<hr/>				
741 mg/kg	13-0863/64	0.044	0.032	
	13-0885/86	0.060	0.050	
	13-0887/88	0.044	0.033	
	13-0907/08	0.053	0.044	
	13-0913/14	0.047		
	<hr/>			
	Mean	0.0495	0.0396	
	SD	0.00686	0.00892	
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***Significantly different from control**

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Appendix H

Individual and Summary of Food Efficiency Data

Toxicity Report No. S.0015656-13, July–August 2013

Table H-1
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rat
14-Day Paired Feed Efficiency
Female Rats

Group	Animal ID	Days 0-1	Days 1-3	Days 3-7	Days 7-13	Total
Control	13-0799/00	0.27	0.09	0.16	0.14	0.15
	13-0811/12	0.24	0.19	0.13	0.13	0.15
	13-0815/16	-0.03	0.15	0.10	0.18	0.13
	13-0821/22	0.09	0.11	0.06	0.23	0.15
	13-0831/32	0.05	0.23	0.05	0.11	0.11
	Mean	0.12	0.15	0.10	0.16	0.14
	SD	0.129	0.056	0.048	0.047	0.018
20 mg/kg	13-0823/24	0.39	0.16	0.07	0.11	0.13
	13-0833/34	0.04	0.02	0.05	0.14	0.09
	13-0835/36	0.20	-0.04	0.14	0.13	0.12
	13-0841/42	-0.01	0.16	0.06	0.09	0.09
	13-0843/44	0.19	0.11	0.01	0.12	0.09
	Mean	0.16	0.08	0.07	0.12	0.10
	SD	0.156	0.092	0.049	0.021	0.019
40 mg/kg	13-0807/08	0.45	0.12	0.13	0.08	0.13
	13-0817/18	-0.12	0.11	0.13	0.12	0.10
	13-0819/20	0.28	0.11	0.11	0.09	0.11
	13-0845/46	0.13	0.00	0.04	0.15	0.09
	13-0847/48	0.26	0.14	0.12	0.05	0.10
	Mean	0.20	0.09	0.11	0.10	0.11
	SD	0.214	0.055	0.039	0.038	0.014
80 mg/kg	13-0797/98	0.47	0.00	0.06	0.10	0.10
	13-0809/10	-0.16	0.10	0.11	0.11	0.09
	13-0827/28	0.41	0.13	0.08	0.13	0.14
	13-0851/52	0.14	-0.03	0.08	0.10	0.08
	13-0853/54	-0.10	0.00	0.07	0.14	0.08
	Mean	0.15	0.04	0.08	0.12	0.10*
	SD	0.285	0.070	0.017	0.019	0.024
159 mg/kg	13-0801/02	0.34	-0.10	0.16	0.02	0.07
	13-0803/04	-0.01	-0.01	0.06	0.10	0.06
	13-0829/30	0.01	0.17	0.03	0.01	0.05
	13-0837/38	0.13	0.18	0.12	0.07	0.11
	13-0849/50	0.00	0.14	0.06	0.03	0.05

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		Mean	0.09	0.07	0.09	0.04	0.07*
		SD	0.150	0.124	0.051	0.038	0.024
318 mg/kg	13-0795/96		-0.15	-0.40	0.18		0.03
	13-0805/06		0.22	-0.06	0.01		
	13-0813/14		0.41	-0.12	-0.03	0.07	0.04
	13-0825/26		-0.22	-0.38			
	13-0839/40		0.44	-0.11	0.08	0.02	0.05
		Mean	0.14	-0.21	0.06	0.05	0.04*
		SD	0.310	0.163	0.093	0.037	0.011

*Significantly different from control

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Table H-2
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rat
14-Day Paired Feed Efficiency
Male Rats

Group	Animal ID	Days 0-1	Days 1-3	Days 3-7	Days 7-13	Total
Control	13-0855/56	0.27	0.24	0.22	0.23	0.23
	13-0873/74	0.22	0.27	0.24	0.23	0.24
	13-0879/80	0.18	0.31	0.26	0.26	0.26
	13-0891/92	0.11	0.32	0.24	0.23	0.24
	13-0901/02	0.36	0.23	0.28	0.20	0.24
	Mean	0.23	0.28	0.25	0.23	0.24
	SD	0.095	0.042	0.021	0.021	0.012
47 mg/kg	13-0861/62	0.18	0.27	0.29	0.25	0.26
	13-0865/66	0.27	0.20	0.22	0.19	0.21
	13-0869/70	0.22	0.20	0.20	0.22	0.21
	13-0889/90	0.11	0.23	0.22	0.22	0.21
	13-0911/12	0.34	0.15	0.24	0.21	0.22
	Mean	0.22	0.21	0.24	0.22	0.22
	SD	0.088	0.047	0.035	0.020	0.022
93 mg/kg	13-0859/60	0.33	0.21	0.21	0.20	0.22
	13-0875/76	0.30	0.17	0.20	0.18	0.19
	13-0881/82	0.46	0.10	0.24	0.20	0.22
	13-0899/00	0.19	0.22	0.24	0.18	0.21
	13-0909/10	0.17	0.19	0.26	0.19	0.21
	Mean	0.29	0.18	0.23	0.19	0.21
	SD	0.117	0.049	0.024	0.009	0.009
185 mg/kg*	13-0867/68	0.18	0.21	0.29	0.16	0.21
	13-0877/78	-0.20	-0.25	0.00	-0.07	-0.09
	13-0883/84	0.19	0.25	0.27	0.05	0.17
	13-0897/98	0.15	0.21	0.13	0.21	0.18
	13-0903/04	0.13	0.15	-0.01	0.19	0.12
	Mean	0.09	0.11	0.13	0.11	0.12*
	SD	0.163	0.206	0.143	0.117	0.121
370 mg/kg	13-0857/58	-0.10	0.16	-0.24		
	13-0871/72	0.47	-0.19	-0.36		
	13-0893/94	0.04	-0.22	0.06		
	13-0895/96	0.03	-0.28			
	13-0905/06	0.08	-0.25			

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	Mean	0.10	-0.16	-0.18
	SD	0.215	0.179	0.212
741 mg/kg	13-0863/64	-0.33	-0.92	
	13-0885/86	0.34	-0.69	
	13-0887/88	-0.06	-0.83	
	13-0907/08	-0.01	-0.62	
	13-0913/14	-0.38		
	Mean	-0.09	-0.77	
	SD	0.288	0.137	

***Significantly different from control**

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Appendix I

Individual and Summary of Urinalysis Data

Table I-1
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Urinalysis
Female Rats

Group	Animal ID	Water Intake (ml)	Urine Volume (ml)	Color	Appearance	Glucose (g/dl)	Bilirubin	Ketone (mg/dl)	Specific Gravity	Blood	pH	Protein (mg/dl)	Urobilinogen (mg/dl)	Nitrites	Leucocytes
0 mg/kg-day	13-0799	10	9.5	light yellow	clear	(-)	(-)	(-)	1.016	(-)	7.0	trace	0.2	(-)	(-)
	13-0800	20	18.0	light yellow	clear	(-)	(-)	(-)	1.014	(-)	7.0	(-)	0.2	(-)	(-)
	13-0811	10	12.5	light yellow	clear	(-)	(-)	(-)	1.013	(-)	7.0	(-)	0.2	(-)	(-)
	13-0812	10	10.5	light yellow	clear	(-)	(-)	(-)	1.020	(-)	6.5	(-)	0.2	(-)	(-)
	13-0815	5	7.5	light yellow	clear	(-)	(-)	(-)	1.025	(-)	7.0	trace	0.2	(-)	(-)
	13-0816	15	11.5	yellow	clear	(-)	(-)	(-)	1.013	(-)	7.0	(-)	0.2	(+)	(-)
	13-0821	10	7.5	yellow	clear	(-)	(-)	(-)	1.026	(-)	7.0	trace	0.2	(-)	(-)
	13-0822	10	8.0	yellow	clear	(-)	(-)	(-)	1.024	(-)	7.0	trace	0.2	(-)	(-)
	13-0831	5	3.0	yellow	clear	(-)	small	(-)	1.035	(-)	6.5	30	0.2	(-)	(-)
	13-0832	5	3.0	yellow	hazy	(-)	(-)	(-)	1.033	(-)	6.5	30	0.2	(-)	(-)
Mean		10.00	9.10						1.022		6.85		0.20		
SD		4.714	4.465						0.0081		0.24		0.000		
	13-0823	10	8.5	light yellow	clear	(-)	(-)	(-)	1.017	(-)	7.5	trace	0.2	(-)	(-)
	13-0824	5	6.0	yellow	clear	(-)	small	(-)	1.030	(-)	7.0	30	0.2	(-)	(-)
	13-0833	0	6.0	yellow	hazy	(-)	small	(-)	1.028	(-)	7.0	trace	0.2	(-)	(-)
	13-0834	5	9.5	light	clear	(-)	(-)	(-)	1.016	(-)	7.5	(-)	0.2	(-)	(-)

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				yellow											
20 mg/kg- day	13-0835	20	13.0	straw	clear	(-)	(-)	(-)	1.013	(-)	7.5	(-)	0.2	(-)	(-)
	13-0836	10	13.5	light	hazy	(-)	(-)	(-)	1.017	(-)	7.5	(-)	0.2	(-)	(-)
	13-0841	5	6.0	yellow	hazy	(-)	(-)	(-)	1.027	(-)	7.0	trace	0.2	(-)	(-)
	13-0842	15	10.5	light	clear	(-)	(-)	(-)	1.020	(-)	7.0	(-)	0.2	(-)	(-)
	13-0843	15	12.5	yellow	clear	(-)	(-)	(-)	1.014	(-)	7.5	trace	0.2	(-)	(-)
	13-0844	15	8.5	straw	clear	(-)	(-)	(-)	1.016	(-)	6.5	(-)	0.2	(+)	(-)
	Mean	10.00	9.40							1.020	7.20			0.20	
		SD	6.236	2.923							0.0062	0.35			0.000
40 mg/kg- day	13-0807	10	8.0	light	clear	(-)	(-)	(-)	1.015	(-)	7.0	trace	0.2	(-)	(-)
	13-0808	15	15.0	yellow	clear	(-)	(-)	(-)	1.012	(-)	7.0	(-)	0.2	(-)	(-)
	13-0817	10	13.0	light	clear	(-)	(-)	(-)	1.016	(-)	7.0	trace	0.2	(-)	(-)
	13-0818	0	4.5	yellow	clear	(-)	small	(-)	1.028	(-)	6.5	trace	0.2	(-)	(-)
	13-0819	15	13.5	light	hazy	(-)	(-)	(-)	1.017	(-)	7.0	trace	0.2	(-)	(-)
	13-0820	10	14.0	yellow	hazy	(-)	(-)	(-)	1.016	(-)	7.5	(-)	0.2	(-)	(-)
	13-0845	15	12.5	light	hazy	(-)	(-)	(-)	1.019	(-)	7.5	trace	0.2	(-)	(-)
	13-0846	15	13.5	yellow	hazy	(-)	(-)	(-)	1.014	(-)	7.0	(-)	0.2	(-)	(-)
	13-0847	5	5.5	yellow	clear	(-)	small	(-)	1.030	(-)	7.0	trace	0.2	(-)	(-)
	13-0848	5	6.5	yellow	hazy	(-)	(-)	(-)	1.027	(-)	7.5	trace	0.2	(-)	(-)
	Mean	10.00	10.60							1.019	7.10			0.20	
		SD	5.270	3.999							0.0065	0.32			0.000

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80 mg/kg- day	13-0797	15	13.0	light yellow	clear	(-)	(-)	(-)	1.009	(-)	8.0	trace	0.2	(-)	(-)
	13-0798	20	14.5	straw	clear	(-)	(-)	(-)	1.010	(-)	7.5	(-)	0.2	(-)	(-)
	13-0809	5	10.0	light yellow	clear	(-)	(-)	(-)	1.018	(-)	7.5	trace	0.2	(-)	(-)
	13-0810	15	11.5	light yellow	clear	(-)	(-)	(-)	1.012	(-)	7.5	trace	0.2	(-)	(-)
	13-0827	5	10.5	light yellow	hazy	(-)	(-)	(-)	1.016	(-)	7.5	(-)	0.2	(-)	(-)
	13-0828	5	5.5	light yellow	hazy	(-)	(-)	(-)	1.021	(-)	7.5	trace	0.2	(-)	(-)
	13-0851	10	8.0	light yellow	hazy	(-)	(-)	(-)	1.020	(-)	7.5	trace	0.2	(-)	(-)
	13-0852	15	13.0	light yellow	hazy	(-)	(-)	(-)	1.012	(-)	7.5	(-)	0.2	(-)	(-)
	13-0853	20	13.0	light yellow	clear	(-)	(-)	(-)	1.011	(-)	8.0	trace	0.2	(-)	(-)
	13-0854	25	20.5	straw	clear	(-)	(-)	(-)	1.010	(-)	7.5	(-)	0.2	(-)	(-)
	Mean	13.50	11.95						1.014		7.60*		0.20		
	SD	7.091	4.031						0.0045		0.21		0.000		
159 mg/kg- day	13-0801	10	13.5	light yellow	hazy	(-)	(-)	(-)	1.011	(-)	7.5	(-)	0.2	(-)	(-)
	13-0802	90	82.0	straw	hazy	(-)	(-)	(-)	1.003	(-)	8.0	(-)	0.2	(+)	(-)
	13-0803	10	14.5	light yellow	clear	(-)	(-)	(-)	1.012	(-)	7.5	trace	0.2	(-)	(-)
	13-0804	20	16.5	light yellow	clear	(-)	(-)	(-)	1.009	(-)	7.5	(-)	0.2	(-)	(-)
	13-0829	5	7.0	light yellow	hazy	(-)	(-)	(-)	1.020	(-)	7.5	trace	0.2	(-)	(-)
	13-0830	10	7.5	light yellow	cloudy	(-)	(-)	(-)	1.015	(-)	8.0	(-)	0.2	(+)	(-)
	13-0837	10	10.0	yellow	hazy	(-)	(-)	(-)	1.019	(-)	7.5	trace	0.2	(-)	(-)
	13-0838	30	28.0	straw	clear	(-)	(-)	(-)	1.009	(-)	7.5	(-)	0.2	(-)	(-)
	13-0849	25	23.5	straw	clear	(-)	(-)	(-)	1.008	(-)	8.0	(-)	0.2	(-)	(-)

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	13-0850	40	26.0	straw	clear	(-)	(-)	(-)	1.006	(-)	7.0	(-)	0.2	(-)	(-)
	Mean	25.00	22.85*						1.011*		7.60*		0.20		
	SD	25.386	22.073						0.0055		0.32		0.000		
	13-0795	20	9.5	straw	clear	(-)	(-)	(-)	1.007	(-)	7.5	trace	0.2	(-)	(-)
	13-0796														
	13-0805														
	13-0806														
318 mg/kg- day										hemolyzed					
	13-0813	10	11.0	light yellow	clear	(-)	(-)	(-)	1.015	zed trace	6.5	trace	0.2	(-)	(-)
	13-0814	30	15.0	light yellow	clear	(-)	(-)	(-)	1.009	(-)	6.5	(-)	0.2	(-)	(-)
	13-0825														
	13-0826														
	13-0839	5	2.5	gold	cloudy	(-)	small	(-)	1.035	large hemolyzed	6.0	100	0.2	(-)	(-)
	13-0840	30	17.5	straw	clear	(-)	(-)	(-)	1.009	zed trace	7.5	(-)	0.2	(-)	(-)
	Mean	19.00	11.10						1.015	*	6.80		0.20		
	SD	11.40	5.76						0.0116		0.67		0.00		

***Significantly different from controls**

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Table I-2
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Urinalysis															
Male Rats															
Group	Animal ID	Water Intake (ml)	Urine Volume (ml)	Color	Appearance	Glucose (g/dl)	Bilirubin	Ketone (mg/dl)	Specific Gravity	Blood	pH	Protein (mg/dl)	Urobilinogen (mg/dl)	Nitrites	Leucocytes
0 mg/kg-day	13-0855	20	32.0	light yellow	hazy	(-)	(-)	trace	1.011	(-)	7.5	30	0.2	(-)	(-)
	13-0856	5	5.0	dark yellow	cloudy	(-)	(-)	small	1.035	(-)	6.5	30	0.2	(-)	(-)
	13-0873	15	18.5	light yellow	hazy	(-)	(-)	(-)	1.012	(-)	7.5	trace	0.2	(-)	(-)
	13-0874	5	8.5	yellow	cloudy	(-)	(-)	(-)	1.025	(-)	7.0	30	0.2	(-)	(-)
	13-0879	0	6.0	yellow	hazy	(-)	(-)	(-)	1.027	(-)	7.0	30	0.2	(+)	(-)
	13-0880	5	7.0	yellow	cloudy	(-)	(-)	(-)	1.023	(-)	7.5	30	0.2	(-)	(-)
	13-0891	5	11.0	yellow	hazy	(-)	(-)	(-)	1.019	(-)	7.0	trace	0.2	(-)	(-)
	13-0892	20	20.0	light yellow	hazy	(-)	(-)	(-)	1.013	(-)	7.5	(-)	0.2	(-)	(-)
	13-0901	10	28.0	yellow	cloudy	(-)	(-)	(-)	1.016	(-)	7.0	trace	0.2	(+)	(-)
	13-0902	10	7.0	gold	cloudy	(-)	(-)	trace	1.028	(-)	7.5	30	0.2	(-)	(-)
	Mean	9.50	14.30						1.021		7.20		0.20		
	SD	6.852	9.762						0.0080		0.35		0.000		
47	13-0861	30	28.5	straw dark	clear	(-)	(-)	trace	1.009	(-)	7.5	trace	0.2	(+)	(-)
	13-0862	5	9.0	yellow	hazy	(-)	small	trace	1.030	(-)	7.0	30	0.2	(-)	(-)
	13-0865	10	11.5	yellow	hazy	(-)	(-)	(-)	1.018	(-)	8.0	trace	0.2	(-)	(-)
	13-0866	10	11.5	yellow	hazy	(-)	(-)	small	1.021	(-)	7.0	30	0.2	(-)	(-)
	13-0869	5	6.0	yellow	hazy	(-)	small	small	1.030	(-)	7.0	30	0.2	(-)	(-)

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mg/kg-day	13-0870	15	17.0	light yellow	hazy	(-)	(-)	(-)	1.012	(-)	7.5	trace	0.2	(-)	(-)
	13-0889	10	12.0	yellow	hazy	(-)	(-)	small	1.018	(-)	7.5	trace	0.2	(-)	(-)
	13-0890	5	11.0	yellow	cloudy	(-)	(-)	(-)	1.021	(-)	7.5	trace	0.2	(+)	(-)
	13-0911	20	21.0	straw	clear	(-)	(-)	trace	1.010	(-)	7.5	trace	0.2	(-)	(-)
	13-0912	5	8.0	gold	cloudy	(-)	(-)	(-)	1.031	(-)	7.0	30	0.2	(-)	(-)
	Mean	11.50	13.55						1.020		7.35		0.20		
93 mg/kg-day	SD	8.182	6.805						0.0083		0.34		0.000		
	13-0859	10	9.0	yellow	cloudy	(-)	(-)	(-)	1.023	(-)	7.5	30	0.2	(-)	(-)
	13-0860	10	12.5	yellow	hazy	(-)	(-)	(-)	1.018	(-)	8.0	30	0.2	(-)	(-)
	13-0875	10	21.5	light yellow	hazy	(-)	(-)	trace	1.013	(-)	7.5	trace	0.2	(-)	(-)
	13-0876	30	27.0	straw	hazy	(-)	(-)	(-)	1.007	(-)	8.0	trace	0.2	(-)	(-)
	13-0881	0	6.5	yellow	cloudy	(-)	small	trace	1.029	(-)	7.0	30	0.2	(-)	(-)
	13-0882	0	10.0	yellow	hazy	(-)	(-)	(-)	1.020	(-)	7.5	trace	0.2	(-)	(-)
	13-0899	20	20.0	light yellow	hazy	(-)	(-)	(-)	1.013	(-)	7.0	trace	0.2	(-)	(-)
	13-0900	25	32.0	light yellow	hazy	(-)	(-)	(-)	1.009	(-)	8.0	(-)	0.2	(-)	(-)
	13-0909	20	18.5	light yellow	hazy	(-)	(-)	(-)	1.013	hemolyzed trace	8.0	trace	0.2	(-)	(-)
	13-0910	5	16.0	light yellow	hazy	(-)	(-)	(-)	1.020	(-)	7.5	30	0.2	(-)	(-)
	Mean	13.00	17.30						1.017		7.60		0.20		
	SD	10.328	8.166						0.0067		0.39		0.000		
	13-0867	15	19.0	straw dark	hazy	(-)	(-)	(-)	1.013	hemolyzed trace	7.5	trace	0.2	(+)	(-)
	13-0868	5	8.5	yellow	cloudy	(-)	(-)	(-)	1.026	(-)	8.0	30	0.2	(-)	(-)

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185 mg/kg- day	13-0877	15	15.0	light yellow	hazy	(-)	(-)	(-)	1.010	(-)	7.0	(-)	0.2	(-)	(-)
	13-0878														
	13-0883	45	43.0	straw	clear	(-)	(-)	(-)	1.006	small	7.0	(-)	0.2	(-)	(-)
	13-0884	5	11.5	yellow	hazy	(-)	(-)	(-)	1.019	(-)	7.5	trace	0.2	(-)	(-)
	13-0897	45	40.0	straw	clear	(-)	(-)	(-)	1.006	(-)	8.0	(-)	0.2	(-)	(-)
	13-0898	35	24.5	straw	clear	(-)	(-)	(-)	1.005	(-)	8.0	trace	0.2	(-)	(-)
	13-0903	10	19.5	light yellow	hazy	(-)	(-)	(-)	1.012	hemolys ed trace	8.0	trace	0.2	(-)	(-)
	13-0904	10	14.5	yellow	cloudy	(-)	(-)	trace	1.022	(-)	7.0	trace	0.2	(-)	(-)
Mean		20.56	21.72							1.013	7.56	0.20			
SD		16.478	12.163							0.0076	0.46	0.000			
370 mg/kg- day	13-0857														
	13-0858														
	13-0871														
	13-0872														
	13-0893														
	13-0894														
	13-0895														
	13-0896														
	13-0905														
	13-0906														
	Mean														
	SD														
	13-0863														
	13-0864														
	13-0885														

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741 mg/kg- day	13-0886
	13-0887
	13-0888
	13-0907
	13-0908
	13-0913
	13-0914
	Mean
	SD
*Significantly different from control	

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Appendix J

Individual and Summary of Organ Mass Data

Table J-1
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Organ Mass
Female Rats

ABSOLUTE ORGAN MASS (GRAMS)											
Group	Animal ID	adrenals	brain	heart	kidneys	liver	ovaries	spleen	thymus	thyroid	uterus
0 mg/kg- day	13-0799	0.096	1.909	1.066	1.937	7.962	0.141	0.665	0.473	0.011	0.361
	13-0800	0.073	1.918	0.999	1.803	7.656	0.174	0.558	0.442	0.015	0.648
	13-0811	0.072	1.800	0.896	1.764	7.442	0.126	0.587	0.310	0.009	0.769
	13-0812	0.085	1.995	0.974	1.971	8.434	0.170	0.569	0.166	0.013	0.387
	13-0815	0.076	1.865	1.227	2.048	10.370	0.166	0.495	0.655	0.015	0.651
	13-0816	0.077	1.840	1.067	1.850	8.355	0.185	0.579	0.382	0.005	0.395
	13-0821	0.067	1.805	0.894	1.614	7.575	0.152	0.507	0.517	0.013	0.461
	13-0822	0.086	2.014	0.968	1.766	7.325	0.126	0.425	0.267	0.011	0.693
	13-0831	0.062	1.828	0.992	1.718	8.115	0.135	0.571	0.460	0.013	0.362
	13-0832	0.089	1.874	1.132	1.725	9.206	0.143	0.590	0.568	0.005	0.516
	Mean	0.0783	1.8848	1.0215	1.8196	8.2440	0.1518	0.5546	0.4240	0.0110	0.5243
	SD	0.0105	0.0744	0.1038	0.1323	0.9352	0.0209	0.0651	0.1463	0.0036	0.1536
	13-0823	0.056	1.876	0.994	1.840	6.986	0.138	0.571	0.332	0.011	0.411
	13-0824	0.076	1.985	0.995	2.069	7.815	0.153	0.515	0.420	0.013	0.604
	13-0833	0.086	1.919	0.943	1.724	7.435	0.132	0.663	0.519	0.010	0.722

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20 mg/kg- day	13-0834	0.066	1.842	0.989	1.651	6.816	0.106	0.460	0.514	0.010	0.423
	13-0835	0.072	1.727	1.067	1.566	7.733	0.162	0.497	0.398	0.005	0.447
	13-0836	0.074	1.910	1.089	2.038	9.121	0.160	0.574	0.467	0.015	0.573
	13-0841	0.068	1.956	0.970	1.834	8.423	0.174	0.488	0.481	0.013	0.53
	13-0842	0.087	1.927	0.905	2.361	8.882	0.153	0.604	0.524	0.009	0.619
	13-0843	0.077	2.005	1.007	1.751	8.154	0.155	0.563	0.726	0.009	0.442
	13-0844	0.076	1.936	1.022	1.774	8.772	0.124	0.575	0.427	0.014	0.621
<hr/>											
	Mean	0.0738	1.9083	0.9981	1.8608	8.0137	0.1457	0.5510	0.4808	0.0110	0.5392
	SD	0.0092	0.0796	0.0540	0.2346	0.7949	0.0204	0.0610	0.1056	0.0030	0.1053
40 mg/kg- day	13-0807	0.079	1.792	1.000	1.757	8.505	0.133	0.480	0.485	0.018	0.476
	13-0808	0.088	1.907	1.033	1.850	7.967	0.131	0.700	0.517	0.016	0.433
	13-0817	0.083	1.928	1.036	1.942	8.171	0.159	0.471	0.537	0.009	0.483
	13-0818	0.082	1.791	1.173	1.937	10.438	0.149	0.581		0.017	0.342
	13-0819	0.085	1.901	1.025	1.814	9.642	0.164	0.566	0.613	0.012	0.675
	13-0820	0.079	1.944	1.060	2.086	10.250	0.157	0.633	0.747	0.005	0.365
	13-0845	0.090	1.866	1.139	1.901	9.596	0.133	0.581*	0.585	0.013	0.567
	13-0846	0.073	1.902	0.936	1.679	7.669	0.151	0.496	0.468	0.012	0.516
	13-0847	0.090	1.944	0.968	1.907	8.745	0.187	0.500	0.538	0.009	0.562
	13-0848	0.081	1.734	0.833	1.650	7.173	0.145	0.452	0.372	0.013	0.477
	Mean	0.0830	1.8709	1.0203	1.8523	8.8156	0.1509	0.5421	0.5402	0.0124	0.4896
	SD	0.0054	0.0734	0.0970	0.1320	1.1171	0.0172	0.0838	0.1044	0.0041	0.0984
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	13-0797	0.069	1.874	0.978	1.619	8.408	0.141	0.510	0.233	0.010	0.366

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80 mg/kg- day	13-0798	0.066	1.923	1.114	1.714	8.150	0.124	0.500	0.437	0.013	0.499
	13-0809	0.082	1.907	0.913	1.718	8.004	0.125	0.561	0.434	0.013	0.532
	13-0810	0.065	1.853	1.142	1.725	8.743	0.160	0.469	0.440	0.018	0.491
	13-0827	0.073	1.941	1.026	1.882	8.537	0.135	0.549	0.576	0.010	0.436
	13-0828	0.091	1.837	1.049	1.935	9.373	0.147	0.676	0.588	0.013	0.531
	13-0851	0.082	1.920	1.000	1.932	8.684	0.131	0.510	0.448	0.009	0.554
	13-0852	0.072	1.921	1.096	1.863	9.361	0.151	0.538	0.660	0.019	0.394
	13-0853	0.083	2.059	0.964	1.722	8.660	0.149	0.513	0.638	0.011	0.625
	13-0854	0.092	1.988	0.937	1.633	8.486	0.143	0.421	0.383	0.012	0.651
<hr/>											
	Mean	0.0775	1.9223	1.0219	1.7743	8.6406	0.1406	0.5247	0.4837	0.0129	0.5079
	SD	0.0099	0.0650	0.0774	0.1184	0.4476	0.0118	0.0667	0.1313	0.0034	0.0919
159 mg/kg- day	13-0801	0.059	1.946	0.959	1.636	8.212	0.148	0.495	0.344	0.019	0.823
	13-0802	0.070	1.971	0.885	1.808	11.380	0.138	0.542	0.327	0.014	0.464
	13-0803	0.060	1.892	0.928	1.807	8.284	0.145	0.512	0.141	0.013	0.541
	13-0804	0.067	1.835	1.003	1.723	8.786	0.111	0.517	0.465	0.018	0.496
	13-0829	0.073	1.849	0.749	1.431	6.557	0.130	0.524	0.427	0.010	0.423
	13-0830	0.086	1.992	1.019	1.671	9.386	0.152	0.572	0.447	0.013	0.559
	13-0837	0.080	1.833	1.081	2.060	11.103	0.179	0.758	0.720	0.014	0.373
	13-0838	0.079	1.874	1.073	2.034	10.466	0.175	0.615	0.621	0.011	0.45
	13-0849	0.059	1.755	0.988	1.722	8.337	0.151	0.538	0.554	0.008	0.375
	13-0850	0.084	1.893	0.957	1.688	9.286	0.143	0.625	0.454	0.011	0.597
	Mean	0.0717	1.8840	0.9642	1.7580	9.1797	0.1472	0.5698	0.4500	0.0130	0.5101
	SD	0.0103	0.0716	0.0969	0.1853	1.4807	0.0198	0.0790	0.1618	0.0033	0.1331

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318 mg/kg- day	13-0795	0.107	1.594	0.867	1.872	8.097	0.108	0.506	0.332	0.013	0.591
	13-0796	0.097	2.049	0.958	1.666	9.314	0.167	0.510	0.195	0.00155*	1.808
	13-0805	0.100	1.880	0.734	1.691	9.077	0.121	0.263	0.165	0.009	0.303
	13-0806	0.091	1.892	0.828	1.479	9.469	0.135	0.386	0.289	0.012	0.399
	13-0813	0.097	1.855	0.913	1.670	9.989	0.110	0.426	0.348	0.004	0.648
	13-0814	0.071	1.775	0.720	1.443	8.732	0.107	0.470	0.303	0.013	0.319
	13-0825	0.065	1.765	0.902	1.437	8.174	0.095	0.336	0.138	0.010	0.406
	13-0826	0.078	1.790	0.782	1.470	10.045	0.121	0.424	0.157	0.017	0.25
	13-0839	0.098	1.870	1.044	1.689	9.171	0.128	0.352	0.321	0.007	0.423
	13-0840	0.086	1.962	0.735	1.540	8.574	0.083	0.438	0.287	0.013	0.417
	Mean	0.0890	1.8432	0.8483*	1.5957*	9.0642	0.1175*	0.4111*	0.2535*	0.0109	0.5564
	SD	0.0137	0.1233	0.1080	0.1436	0.6777	0.0232	0.0782	0.0805	0.0037	0.4565

***Significantly different from control**

Table J-2
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Organ Mass
Male Rats

ABSOLUTE ORGAN MASS (GRAMS)											
Group	Animal ID	adrenals	brain	heart	kidneys	epididymi des	liver	spleen	testes	thymus	thyroid
0 mg/kg- day	13-0855	0.064	2.196	1.553	2.985	0.998	12.684	0.740	3.475	0.646	0.005
	13-0856	0.051	2.004	1.426	2.596	0.869	11.736	0.607	2.855	0.465	0.023
	13-0873	0.049	2.056	1.602	2.806	1.066	15.661	1.128*	3.831	0.630	0.013
	13-0874	0.056	2.004	1.398	2.694	0.924	12.365	0.895	3.204	0.411	0.018
	13-0879	0.086	2.041	1.308	2.473	0.913	11.934	0.723	3.276	0.416	0.013
	13-0880	0.065	2.019	1.599	3.004	1.065	14.579	0.883	3.066	0.457	0.012
	13-0891	0.076	2.283	1.607	2.868	0.909	13.642	1.034	3.348	0.946	0.015
	13-0892	0.075	1.967	1.538	2.635	0.893	13.304	0.926	3.020	0.502	0.012
	13-0901	0.082	2.196	1.694	3.065	0.945	16.800	0.955	3.414	0.712	0.013
	13-0902	0.069	1.650	1.308	2.164	1.027	11.375	0.619	2.871	0.491	0.010
	Mean	0.0673	2.0416	1.5033	2.7290	0.9609	13.4080	0.8202	3.2360	0.5676	0.0134
	SD	0.0127	0.1727	0.1346	0.2773	0.0725	1.7867	0.1527	0.3004	0.1682	0.0047
	13-0861	0.067	2.130	1.315	2.604	0.923	14.005	0.768	3.439	0.619	0.016
	13-0862	0.067	2.150	1.376	2.675	0.825	13.043	0.536	3.271	0.245	0.017
	13-0865	0.052	1.816	1.083	2.223	0.926	10.153	0.597	3.090	0.477	0.012
	13-0866	0.088	1.977	1.514	3.224	0.808	15.976	0.780	3.052	0.431	0.018

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47 mg/kg-day	13-0869	0.088	1.951	1.351	2.353	0.860	12.568	0.703	3.448	0.462	0.014
	13-0870	0.063	1.916	1.130	2.280	0.844	10.605	0.855	3.019	0.563	0.016
	13-0889	0.059	2.015	1.356	2.649	0.823	12.331	0.862	2.964	0.626	0.012
	13-0890	0.062	1.833	1.227	2.786	1.011	11.939	0.835	3.534	0.419	0.013
	13-0911	0.058	2.082	1.408	2.944	1.078	14.210	1.001	3.176	0.565	0.012
	13-0912	0.065	2.042	1.295	2.820	0.981	13.766	0.641	2.977	0.522	0.020
Mean		0.0669	1.9912	1.3055	2.6558	0.9079	12.8596	0.7578	3.1970	0.4929	0.0151
SD		0.0120	0.1150	0.1292	0.3115	0.0918	1.7424	0.1405	0.2129	0.1138	0.0028
93 mg/kg-day	13-0859	0.079	2.158	1.326	2.593	0.872	12.935	0.681	3.197	0.420	0.016
	13-0860	0.045	1.772	1.100	2.251	0.893	12.078	0.773	2.811	0.425	0.011
	13-0875	0.071	1.931	1.271	2.664	0.931	12.211	0.556	3.025	0.283	0.015
	13-0876	0.063	2.040	1.243	2.354	0.905	11.640	0.512	3.219	0.397	0.008
	13-0881	0.060	2.167	1.335	2.625	0.977	11.172	0.666	3.249	0.536	0.020
	13-0882	0.072	2.036	1.385	2.699	0.856	11.652	0.892	3.318	0.584	0.012
	13-0899	0.070	2.071	1.564	2.884	1.007	15.534	1.095	3.115	0.583	0.016
	13-0900	0.042	1.999	1.356	2.882	1.114	13.339	0.875	3.358	0.502	0.013
	13-0909	0.056	1.966	1.433	2.868	1.121	16.094	0.862	3.399	0.498	0.012
	13-0910	0.055	2.085	1.552	3.350	0.996	14.521	0.872	3.329	0.566	0.015
Mean		0.0613	2.0225	1.3565	2.7170	0.9672	13.1176	0.7784	3.2020	0.4794	0.0138
SD		0.0121	0.1159	0.1396	0.3081	0.0942	1.7246	0.1766	0.1786	0.0972	0.0033
	13-0867	0.060	1.990	1.058	2.025	0.910	9.774	0.582	3.330	0.405	0.010
	13-0868	0.060	1.951	1.264	2.599	0.903	14.487	0.730	3.215	0.420	0.017
	13-0877	0.072	1.938	0.992	2.145	0.785	11.275	0.640	2.811	0.143	0.010
	13-0878	0.057	1.883	0.681	2.591	0.625	6.793	0.182	2.936	0.057	0.015

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185 mg/kg- day	13-0883	0.093	2.012	1.078	2.379	0.735	11.913	0.552	2.795	0.357	0.010
	13-0884	0.073	1.853	1.166	2.497	1.014	10.555	0.639	3.417	0.416	0.012
	13-0897	0.045	1.959	1.400	2.714	0.859	11.929	0.662	3.040	0.290	0.017
	13-0898	0.068	1.915	1.426	2.665	0.904	15.935	0.890	3.266	0.472	0.014
	13-0903	0.033*	2.015	0.876	2.230	1.002	10.422	0.605	3.310	0.344	0.012
	13-0904	0.084	1.968	1.142	3.069	1.004	12.176	0.739	3.233	0.489	0.017
	Mean	0.0680	1.9484	1.1083*	2.4914	0.8741	11.5259	0.6221*	3.1353	0.3393*	0.0134
	SD	0.0146	0.0530	0.2281	0.3079	0.1271	2.5086	0.1825	0.2237	0.1405	0.0031
370 mg/kg- day	13-0857	0.077	1.874	0.906	2.072	0.755	9.653	0.232	3.117	0.219	0.013
	13-0858	0.046	2.010	0.899	1.785	0.746	8.861	0.400	3.760	0.249	0.013
	13-0871										
	13-0872	0.091	1.914	1.146	2.277	0.642	10.296	0.426	3.283	0.230	0.015
	13-0893	0.072	1.902	0.913	2.000	0.813	9.756	0.354	3.512	0.197	0.014
	13-0894	0.092	1.891	1.634	2.472	0.695	11.613	0.434	3.114	0.218	0.018
	13-0895	0.079	1.787	1.422	1.987	0.648	11.932	0.355	3.580	0.119	0.013
	13-0896	0.069	2.033	1.293	3.905	0.704	16.263	0.467	3.188	0.209	0.014
	13-0905	0.058	1.834	1.049	1.819	0.613	10.526	0.297	3.407	0.176	0.014
	13-0906	0.088	1.947	0.967	2.931	0.627	12.628	0.445	2.983	0.407	0.008
	Mean	0.0747	1.9102	1.1366*	2.3609	0.6937*	11.2809	0.3789*	3.3271	0.2249*	0.0135
	SD	0.0154	0.0784	0.2621	0.6808	0.0676	2.2232	0.0769	0.2552	0.0779	0.0024
	13-0863	0.053	1.895	1.128	2.147	0.519	10.426	0.327	3.072	0.256	0.011
	13-0864	0.040	1.829	1.341	2.073	0.724	9.213	0.316	3.410	0.099	0.011

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741 mg/kg- day	13-0885	0.062	1.841	1.025	1.885	0.637	10.125	0.401	3.131	0.185	0.012
	13-0886										
	13-0887	0.067	1.814	1.809	2.322	0.542	11.437	0.496	3.130	0.247	0.014
	13-0888	0.069	1.969	1.505	2.244	0.630	11.850	0.480	3.513	0.237	0.013
	13-0907	0.064	1.950	1.642	1.809	0.619	9.722	0.322	2.791	0.179	0.009
	13-0908	0.070	1.879	1.098	2.052	0.594	10.758	0.372	2.971	0.235	0.022
	13-0913										
	13-0914	0.051	1.783	1.033	1.874	0.666	11.990	0.350	2.746	0.282	0.013
	Mean	0.0595	1.8700*	1.3226	2.0508*	0.6164*	10.6901*	0.3830*	3.0955	0.2150*	0.0130
	SD	0.0105	0.0656	0.3007	0.1843	0.0657	1.0075	0.0708	0.2690	0.0582	0.0037

*Significantly different from control

Table J-3
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Organ Mass/Body Mass
Female Rats

ORGAN MASS/BODY MASS											
Group	Animal ID	adrenals	brain	heart	kidneys	liver	ovaries	spleen	thymus	thyroid	uterus
0 mg/kg-day	13-0799	0.00040	0.0079	0.0044	0.0080	0.0328	0.0006	0.0027	0.0019	0.000044	0.0015
	13-0800	0.00031	0.0081	0.0042	0.0076	0.0322	0.0007	0.0023	0.0019	0.000062	0.0027
	13-0811	0.00032	0.0080	0.0040	0.0079	0.0331	0.0006	0.0026	0.0014	0.000040	0.0034
	13-0812	0.00036	0.0083	0.0041	0.0082	0.0353	0.0007	0.0024	0.0007	0.000054	0.0016
	13-0815	0.00027	0.0066	0.0043	0.0072	0.0367	0.0006	0.0018	0.0023	0.000054	0.0023
	13-0816	0.00031	0.0073	0.0043	0.0074	0.0333	0.0007	0.0023	0.0015	0.000019	0.0016
	13-0821	0.00029	0.0079	0.0039	0.0071	0.0333	0.0007	0.0022	0.0023	0.000057	0.0020
	13-0822	0.00036	0.0085	0.0041	0.0075	0.0309	0.0005	0.0018	0.0011	0.000048	0.0029
	13-0831	0.00025	0.0075	0.0041	0.0070	0.0332	0.0006	0.0023	0.0019	0.000052	0.0015
	13-0832	0.00037	0.0078	0.0047	0.0071	0.0381	0.0006	0.0024	0.0024	0.000023	0.0021
	Mean	0.000323	0.00779	0.00420	0.00750	0.03390	0.00063	0.00229	0.00174	0.0000454	0.00217
	SD	0.000046	0.00055	0.00023	0.00041	0.00215	0.00008	0.00031	0.00055	0.0000144	0.00067
20 mg/kg-day	13-0823	0.00024	0.0082	0.0043	0.0080	0.0305	0.0006	0.0025	0.0015	0.000050	0.0018
	13-0824	0.00033	0.0087	0.0043	0.0090	0.0342	0.0007	0.0023	0.0018	0.000056	0.0026
	13-0833	0.00040	0.0089	0.0044	0.0080	0.0345	0.0006	0.0031	0.0024	0.000048	0.0034
	13-0834	0.00028	0.0079	0.0043	0.0071	0.0294	0.0005	0.0020	0.0022	0.000044	0.0018
	13-0835	0.00033	0.0078	0.0048	0.0071	0.0349	0.0007	0.0022	0.0018	0.000022	0.0020
	13-0836	0.00029	0.0075	0.0043	0.0080	0.0359	0.0006	0.0023	0.0018	0.000060	0.0023
	13-0841	0.00029	0.0084	0.0042	0.0079	0.0363	0.0007	0.0021	0.0021	0.000055	0.0023
	13-0842	0.00034	0.0076	0.0036	0.0093	0.0349	0.0006	0.0024	0.0021	0.000037	0.0024

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	13-0843	0.00032	0.0084	0.0042	0.0073	0.0342	0.0007	0.0024	0.0030	0.000037	0.0019
	13-0844	0.00032	0.0080	0.0042	0.0074	0.0364	0.0005	0.0024	0.0018	0.000058	0.0026
	Mean	0.000315	0.00815	0.00426	0.00792	0.03412	0.00062	0.00235	0.00205	0.0000466	0.00230
	SD	0.000041	0.00046	0.00031	0.00076	0.00235	0.00009	0.00029	0.00044	0.0000119	0.00048
40 mg/kg-day	13-0807	0.00032	0.0073	0.0041	0.0071	0.0346	0.0005	0.0020	0.0020	0.000075	0.0019
	13-0808	0.00037	0.0080	0.0043	0.0077	0.0333	0.0005	0.0029	0.0022	0.000066	0.0018
	13-0817	0.00037	0.0085	0.0046	0.0086	0.0361	0.0007	0.0021	0.0024	0.000041	0.0021
	13-0818	0.00033	0.0072	0.0047	0.0078	0.0418	0.0006	0.0023	0.0000	0.000069	0.0014
	13-0819	0.00034	0.0076	0.0041	0.0073	0.0387	0.0007	0.0023	0.0025	0.000048	0.0027
	13-0820	0.00030	0.0073	0.0040	0.0078	0.0384	0.0006	0.0024	0.0028	0.000018	0.0014
	13-0845	0.00036	0.0075	0.0046	0.0076	0.0385	0.0005		0.0023	0.000050	0.0023
	13-0846	0.00034	0.0089	0.0044	0.0079	0.0361	0.0007	0.0023	0.0022	0.000057	0.0024
	13-0847	0.00037	0.0079	0.0040	0.0078	0.0357	0.0008	0.0020	0.0022	0.000036	0.0023
	13-0848	0.00036	0.0076	0.0037	0.0072	0.0315	0.0006	0.0020	0.0016	0.000056	0.0021
	Mean	0.000345	0.00778	0.00423	0.00768	0.03645	0.00063	0.00225	0.00201	0.0000517	0.00204
	SD	0.000024	0.00057	0.00033	0.00041	0.00300	0.00008	0.00030	0.00077	0.0000169	0.00043
80 mg/kg-day	13-0797	0.00030	0.0083	0.0043	0.0071	0.0371	0.0006	0.0022	0.0010	0.000044	0.0016
	13-0798	0.00029	0.0085	0.0049	0.0076	0.0361	0.0005	0.0022	0.0019	0.000059	0.0022
	13-0809	0.00035	0.0082	0.0039	0.0074	0.0346	0.0005	0.0024	0.0019	0.000058	0.0023
	13-0810	0.00029	0.0084	0.0052	0.0078	0.0394	0.0007	0.0021	0.0020	0.000083	0.0022
	13-0827	0.00030	0.0080	0.0042	0.0078	0.0353	0.0006	0.0023	0.0024	0.000043	0.0018
	13-0828	0.00040	0.0080	0.0046	0.0084	0.0408	0.0006	0.0029	0.0026	0.000056	0.0023
	13-0851	0.00036	0.0084	0.0044	0.0085	0.0381	0.0006	0.0022	0.0020	0.000041	0.0024
	13-0852	0.00029	0.0076	0.0043	0.0074	0.0371	0.0006	0.0021	0.0026	0.000075	0.0016
	13-0853	0.00036	0.0089	0.0042	0.0074	0.0373	0.0006	0.0022	0.0027	0.000045	0.0027
	13-0854	0.00043	0.0092	0.0044	0.0076	0.0394	0.0007	0.0020	0.0018	0.000055	0.0030
	Mean	0.000337	0.00835	0.00444	0.00770	0.03751	0.00061	0.00227	0.00209	0.0000559	0.00222
	SD	0.000049	0.00046	0.00036	0.00044	0.00196	0.00006	0.00026	0.00051	0.0000140	0.00046

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159 mg/kg- day	13-0801	0.00027	0.0088	0.0044	0.0074	0.0373	0.0007	0.0022	0.0016	0.000085	0.0037
	13-0802	0.00030	0.0085	0.0038	0.0078	0.0491	0.0006	0.0023	0.0014	0.000059	0.0020
	13-0803	0.00029	0.0091	0.0045	0.0087	0.0399	0.0007	0.0025	0.0007	0.000065	0.0026
	13-0804	0.00029	0.0080	0.0044	0.0075	0.0385	0.0005	0.0023	0.0020	0.000077	0.0022
	13-0829	0.00036	0.0092	0.0037	0.0071	0.0325	0.0006	0.0026	0.0021	0.000047	0.0021
	13-0830	0.00037	0.0086	0.0044	0.0072	0.0406	0.0007	0.0025	0.0019	0.000056	0.0024
	13-0837	0.00030	0.0068	0.0040	0.0076	0.0410	0.0007	0.0028	0.0027	0.000050	0.0014
	13-0838	0.00030	0.0071	0.0041	0.0077	0.0398	0.0007	0.0023	0.0024	0.000044	0.0017
	13-0849	0.00027	0.0079	0.0045	0.0078	0.0376	0.0007	0.0024	0.0025	0.000035	0.0017
	13-0850	0.00037	0.0082	0.0042	0.0073	0.0404	0.0006	0.0027	0.0020	0.000050	0.0026
	Mean	0.000311	0.00823	0.00419	0.00763	0.03967*	0.00064	0.00247	0.00192	0.0000567	0.00224
	SD	0.000040	0.00080	0.00028	0.00045	0.00416	0.00006	0.00019	0.00058	0.0000154	0.00066
	13-0795	0.00049	0.0073	0.0040	0.0086	0.0373	0.0005	0.0023	0.0015	0.000058	0.0027
	13-0796	0.00042	0.0088	0.0041	0.0071	0.0399	0.0007	0.0022	0.0008		0.0077
	13-0805	0.00047	0.0089	0.0035	0.0080	0.0429	0.0006	0.0012	0.0008	0.000044	0.0014
	13-0806	0.00041	0.0086	0.0038	0.0067	0.0430	0.0006	0.0018	0.0013	0.000053	0.0018
318 mg/kg- day	13-0813	0.00043	0.0082	0.0041	0.0074	0.0443	0.0005	0.0019	0.0015	0.000019	0.0029
	13-0814	0.00034	0.0086	0.0035	0.0070	0.0422	0.0005	0.0023	0.0015	0.000065	0.0015
	13-0825	0.00034	0.0093	0.0047	0.0075	0.0429	0.0005	0.0018	0.0007	0.000050	0.0021
	13-0826	0.00038	0.0086	0.0038	0.0071	0.0485	0.0006	0.0020	0.0008	0.000080	0.0012
	13-0839	0.00042	0.0080	0.0045	0.0072	0.0391	0.0005	0.0015	0.0014	0.000032	0.0018
	13-0840	0.00041	0.0093	0.0035	0.0073	0.0405	0.0004	0.0021	0.0014	0.000063	0.0020
	Mean	0.000411*	0.00855	0.00393	0.00739	0.04205*	0.00054	0.00190*	0.00117	0.0000515	0.00252
	SD	0.000049	0.00059	0.00043	0.00055	0.00313	0.00009	0.00035	0.00035	0.0000184	0.00191

*Significantly different from control

Table J-4
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Organ Mass/Body Mass
Male Rats

ORGAN MASS/BODY MASS											
Group	Animal ID	adrenals	brain	heart	kidneys	epididymides	liver	spleen	testes	thymus	thyroid
0 mg/kg-day	13-0855	0.00019	0.0064	0.0046	0.0088	0.0029	0.0372	0.0022	0.0102	0.0019	0.000016
	13-0856	0.00015	0.0060	0.0043	0.0078	0.0026	0.0351	0.0018	0.0085	0.0014	0.000068
	13-0873	0.00013	0.0056	0.0044	0.0076	0.0029	0.0426		0.0104	0.0017	0.000034
	13-0874	0.00016	0.0058	0.0041	0.0078	0.0027	0.0360	0.0026	0.0093	0.0012	0.000054
	13-0879	0.00027	0.0065	0.0042	0.0079	0.0029	0.0380	0.0023	0.0104	0.0013	0.000041
	13-0880	0.00017	0.0054	0.0043	0.0081	0.0029	0.0392	0.0024	0.0083	0.0012	0.000032
	13-0891	0.00021	0.0063	0.0044	0.0079	0.0025	0.0375	0.0028	0.0092	0.0026	0.000041
	13-0892	0.00021	0.0055	0.0043	0.0074	0.0025	0.0371	0.0026	0.0084	0.0014	0.000034
	13-0901	0.00020	0.0053	0.0041	0.0074	0.0023	0.0406	0.0023	0.0082	0.0017	0.000031
	13-0902	0.00022	0.0053	0.0042	0.0069	0.0033	0.0365	0.0020	0.0092	0.0016	0.000032
	Mean	0.00019	0.00582	0.00427	0.00775	0.00275	0.03799	0.00233	0.00923	0.00160	0.000038
	SD	0.00004	0.00047	0.00015	0.00048	0.00029	0.00225	0.00032	0.00087	0.00042	0.000014
47 mg/kg-day	13-0861	0.00019	0.0061	0.0038	0.0075	0.0026	0.0401	0.0022	0.0098	0.0018	0.000046
	13-0862	0.00019	0.0060	0.0038	0.0075	0.0023	0.0364	0.0015	0.0091	0.0007	0.000047
	13-0865	0.00018	0.0061	0.0037	0.0075	0.0031	0.0343	0.0020	0.0104	0.0016	0.000042
	13-0866	0.00024	0.0055	0.0042	0.0090	0.0022	0.0444	0.0022	0.0085	0.0012	0.000050
	13-0869	0.00028	0.0062	0.0043	0.0075	0.0027	0.0401	0.0022	0.0110	0.0015	0.000046
	13-0870	0.00020	0.0061	0.0036	0.0072	0.0027	0.0335	0.0027	0.0095	0.0018	0.000051
	13-0889	0.00017	0.0057	0.0038	0.0075	0.0023	0.0348	0.0024	0.0084	0.0018	0.000035
	13-0890	0.00018	0.0055	0.0037	0.0083	0.0030	0.0356	0.0025	0.0105	0.0012	0.000039
	13-0911	0.00016	0.0057	0.0039	0.0081	0.0030	0.0390	0.0027	0.0087	0.0016	0.000032

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	13-0912	0.00018	0.0057	0.0036	0.0078	0.0027	0.0381	0.0018	0.0082	0.0014	0.000056
	Mean	0.00020	0.00585	0.00383	0.00777	0.00267	0.03762	0.00223	0.00943	0.00145	0.000044
	SD	0.00004	0.00028	0.00025	0.00053	0.00031	0.00337	0.00039	0.00099	0.00034	0.000008
93 mg/kg-day	13-0859	0.00024	0.0066	0.0041	0.0079	0.0027	0.0396	0.0021	0.0098	0.0013	0.000048
	13-0860	0.00015	0.0058	0.0036	0.0074	0.0029	0.0395	0.0025	0.0092	0.0014	0.000035
	13-0875	0.00023	0.0061	0.0040	0.0085	0.0030	0.0389	0.0018	0.0096	0.0009	0.000048
	13-0876	0.00020	0.0065	0.0039	0.0075	0.0029	0.0368	0.0016	0.0102	0.0013	0.000025
	13-0881	0.00018	0.0065	0.0040	0.0078	0.0029	0.0333	0.0020	0.0097	0.0016	0.000060
	13-0882	0.00021	0.0061	0.0041	0.0081	0.0026	0.0348	0.0027	0.0099	0.0017	0.000036
	13-0899	0.00019	0.0056	0.0042	0.0078	0.0027	0.0421	0.0030	0.0084	0.0016	0.000044
	13-0900	0.00013	0.0061	0.0041	0.0088	0.0034	0.0407	0.0027	0.0102	0.0015	0.000040
	13-0909	0.00015	0.0054	0.0040	0.0079	0.0031	0.0444	0.0024	0.0094	0.0014	0.000034
	13-0910	0.00014	0.0054	0.0040	0.0087	0.0026	0.0379	0.0023	0.0087	0.0015	0.000039
	Mean	0.00018	0.00601	0.00401	0.00804	0.00287	0.03879	0.00229	0.00951	0.00141	0.000041
	SD	0.00004	0.00043	0.00017	0.00049	0.00025	0.00330	0.00043	0.00060	0.00023	0.000009
185 mg/kg-day	13-0867	0.00020	0.0066	0.0035	0.0067	0.0030	0.0323	0.0019	0.0110	0.0013	0.000032
	13-0868	0.00017	0.0056	0.0036	0.0075	0.0026	0.0416	0.0021	0.0092	0.0012	0.000050
	13-0877	0.00026	0.0071	0.0036	0.0078	0.0029	0.0412	0.0023	0.0103	0.0005	0.000038
	13-0878	0.00026	0.0085	0.0031	0.0116	0.0028	0.0305	0.0008	0.0132	0.0003	0.000067
	13-0883	0.00030	0.0066	0.0035	0.0077	0.0024	0.0388	0.0018	0.0091	0.0012	0.000032
	13-0884	0.00023	0.0058	0.0036	0.0077	0.0031	0.0328	0.0020	0.0106	0.0013	0.000036
	13-0897	0.00015	0.0065	0.0047	0.0090	0.0029	0.0397	0.0022	0.0101	0.0010	0.000055
	13-0898	0.00020	0.0056	0.0042	0.0078	0.0026	0.0464	0.0026	0.0095	0.0014	0.000040
	13-0903		0.0073	0.0032	0.0081	0.0036	0.0376	0.0022	0.0119	0.0012	0.000044
	13-0904	0.00025	0.0058	0.0034	0.0090	0.0030	0.0358	0.0022	0.0095	0.0014	0.000051
	Mean	0.00022	0.00652	0.00363	0.00830	0.00289	0.03767	0.00201	0.01045	0.00108*	0.000045
	SD	0.00005	0.00091	0.00047	0.00136	0.00034	0.00492	0.00047	0.00130	0.00039	0.000011
	13-0857	0.00031	0.0075	0.0036	0.0083	0.0030	0.0385	0.0009	0.0124	0.0009	0.000053

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370 mg/kg-day	13-0858	0.00017	0.0073	0.0033	0.0065	0.0027	0.0322	0.0015	0.0136	0.0009	0.000047
	13-0871										
	13-0872	0.00033	0.0070	0.0042	0.0084	0.0024	0.0378	0.0016	0.0121	0.0008	0.000055
	13-0893	0.00029	0.0076	0.0037	0.0080	0.0033	0.0390	0.0014	0.0141	0.0008	0.000055
	13-0894	0.00033	0.0068	0.0059	0.0089	0.0025	0.0417	0.0016	0.0112	0.0008	0.000063
	13-0895	0.00026	0.0059	0.0047	0.0065	0.0021	0.0391	0.0012	0.0117	0.0004	0.000041
	13-0896	0.00025	0.0074	0.0047	0.0143	0.0026	0.0594	0.0017	0.0116	0.0008	0.000052
	13-0905	0.00022	0.0070	0.0040	0.0069	0.0023	0.0402	0.0011	0.0130	0.0007	0.000053
	13-0906	0.00033	0.0073	0.0036	0.0110	0.0024	0.0473	0.0017	0.0112	0.0015	0.000032
Mean		0.00028*	0.00709*	0.00418	0.00874	0.00258	0.04170	0.00140*	0.01233*	0.00084*	0.000050
SD		0.00006	0.00053	0.00080	0.00249	0.00036	0.00772	0.00027	0.00104	0.00030	0.000009
741 mg/kg-day	13-0863	0.00021	0.0075	0.0045	0.0085	0.0021	0.0412	0.0013	0.0121	0.0010	0.000042
	13-0864	0.00020	0.0091	0.0067	0.0103	0.0036	0.0460	0.0016	0.0170	0.0005	0.000057
	13-0885	0.00024	0.0072	0.0040	0.0073	0.0025	0.0394	0.0016	0.0122	0.0007	0.000048
	13-0886										
	13-0887	0.00025	0.0068	0.0067	0.0087	0.0020	0.0427	0.0019	0.0117	0.0009	0.000051
	13-0888	0.00026	0.0074	0.0056	0.0084	0.0024	0.0444	0.0018	0.0132	0.0009	0.000047
	13-0907	0.00024	0.0072	0.0061	0.0067	0.0023	0.0361	0.0012	0.0104	0.0007	0.000033
	13-0908	0.00029	0.0077	0.0045	0.0084	0.0024	0.0442	0.0015	0.0122	0.0010	0.000089
	13-0913										
Mean		0.00024	0.00747*	0.00526*	0.00820	0.00248	0.04250	0.00152*	0.01241*	0.00084*	0.000052
SD		0.00003	0.00074	0.00117	0.00113	0.00050	0.00345	0.00023	0.00207	0.00020	0.000016

*Significantly different from control

Table J-5
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Organ Mass/Brain Mass
Female Rats

ORGAN MASS/BRAIN MASS										
Group	Animal ID	adrenals	heart	kidneys	liver	ovaries	spleen	thymus	thyroid	uterus
0 mg/kg-day	13-0799	0.050	0.558	1.015	4.171	0.074	0.348	0.248	0.0056	0.189
	13-0800	0.038	0.521	0.940	3.992	0.091	0.291	0.230	0.0077	0.338
	13-0811	0.040	0.498	0.980	4.134	0.070	0.326	0.172	0.0050	0.427
	13-0812	0.043	0.488	0.988	4.228	0.085	0.285	0.083	0.0065	0.194
	13-0815	0.041	0.658	1.098	5.560	0.089	0.265	0.351	0.0083	0.349
	13-0816	0.042	0.580	1.005	4.541	0.101	0.315	0.208	0.0026	0.215
	13-0821	0.037	0.495	0.894	4.197	0.084	0.281	0.286	0.0072	0.255
	13-0822	0.043	0.481	0.877	3.637	0.063	0.211	0.133	0.0057	0.344
	13-0831	0.034	0.543	0.940	4.439	0.074	0.312	0.252	0.0070	0.198
	13-0832	0.047	0.604	0.920	4.912	0.076	0.315	0.303	0.0029	0.275
	Mean	0.0415	0.5426	0.9658	4.3811	0.0806	0.2950	0.2266	0.0058	0.2785
	SD	0.0048	0.0580	0.0655	0.5343	0.0113	0.0382	0.0808	0.0019	0.0824
20 mg/kg-day	13-0823	0.030	0.530	0.981	3.724	0.074	0.304	0.177	0.0061	0.219
	13-0824	0.038	0.501	1.042	3.937	0.077	0.259	0.212	0.0065	0.304
	13-0833	0.045	0.491	0.898	3.874	0.069	0.345	0.270	0.0053	0.376
	13-0834	0.036	0.537	0.896	3.700	0.058	0.250	0.279	0.0055	0.230
	13-0835	0.042	0.618	0.907	4.478	0.094	0.288	0.230	0.0028	0.259
	13-0836	0.039	0.570	1.067	4.775	0.084	0.301	0.245	0.0080	0.300
	13-0841	0.035	0.496	0.938	4.306	0.089	0.249	0.246	0.0065	0.271
	13-0842	0.045	0.470	1.225	4.609	0.079	0.313	0.272	0.0049	0.321
	13-0843	0.038	0.502	0.873	4.067	0.077	0.281	0.362	0.0044	0.220

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	13-0844	0.039	0.528	0.916	4.531	0.064	0.297	0.221	0.0072	0.321
	Mean	0.0387	0.5243	0.9744	4.2002	0.0764	0.2888	0.2514	0.0057	0.2821
	SD	0.0046	0.0434	0.1093	0.3896	0.0111	0.0303	0.0499	0.0015	0.0515
40 mg/kg- day	13-0807	0.044	0.558	0.980	4.746	0.074	0.268	0.271	0.0103	0.266
	13-0808	0.046	0.542	0.970	4.178	0.069	0.367	0.271	0.0082	0.227
	13-0817	0.043	0.537	1.007	4.238	0.082	0.244	0.279	0.0048	0.251
	13-0818	0.046	0.655	1.082	5.828	0.083	0.324	0.000	0.0096	0.191
	13-0819	0.045	0.539	0.954	5.072	0.086	0.298	0.322	0.0063	0.355
	13-0820	0.041	0.545	1.073	5.273	0.081	0.326	0.384	0.0025	0.188
	13-0845	0.048	0.610	1.019	5.143	0.071		0.314	0.0067	0.304
	13-0846	0.038	0.492	0.883	4.032	0.079	0.261	0.246	0.0064	0.271
	13-0847	0.046	0.498	0.981	4.498	0.096	0.257	0.277	0.0045	0.289
	13-0848	0.047	0.480	0.952	4.137	0.084	0.261	0.215	0.0074	0.275
	Mean	0.0444	0.5457	0.9901	4.7144	0.0806	0.2895	0.2578	0.0067	0.2616
	SD	0.0030	0.0536	0.0589	0.5986	0.0079	0.0416	0.1016	0.0024	0.0509
80 mg/kg- day	13-0797	0.037	0.522	0.864	4.487	0.075	0.272	0.124	0.0053	0.195
	13-0798	0.034	0.579	0.891	4.238	0.064	0.260	0.227	0.0069	0.259
	13-0809	0.043	0.479	0.901	4.197	0.066	0.294	0.228	0.0071	0.279
	13-0810	0.035	0.616	0.931	4.718	0.086	0.253	0.237	0.0099	0.265
	13-0827	0.038	0.529	0.970	4.398	0.070	0.283	0.297	0.0054	0.225
	13-0828	0.050	0.571	1.053	5.102	0.080	0.368	0.320	0.0070	0.289
	13-0851	0.043	0.521	1.006	4.523	0.068	0.266	0.233	0.0048	0.289
	13-0852	0.037	0.571	0.970	4.873	0.079	0.280	0.344	0.0099	0.205
	13-0853	0.040	0.468	0.836	4.206	0.072	0.249	0.310	0.0051	0.304
	13-0854	0.046	0.471	0.821	4.269	0.072	0.212	0.193	0.0060	0.327
	Mean	0.0403	0.5327	0.9244	4.5011	0.0732	0.2737	0.2513	0.0067	0.2637
	SD	0.0050	0.0507	0.0754	0.3093	0.0069	0.0402	0.0666	0.0019	0.0432

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159 mg/kg-day	13-0801	0.030	0.493	0.841	4.220	0.076	0.254	0.177	0.0096	0.423
	13-0802	0.036	0.449	0.917	5.774	0.070	0.275	0.166	0.0069	0.235
	13-0803	0.032	0.490	0.955	4.378	0.077	0.271	0.075	0.0071	0.286
	13-0804	0.037	0.547	0.939	4.788	0.060	0.282	0.253	0.0096	0.270
	13-0829	0.039	0.405	0.774	3.546	0.070	0.283	0.231	0.0052	0.229
	13-0830	0.043	0.512	0.839	4.712	0.076	0.287	0.224	0.0065	0.281
	13-0837	0.044	0.590	1.124	6.057	0.098	0.414	0.393	0.0074	0.203
	13-0838	0.042	0.573	1.085	5.585	0.093	0.328	0.331	0.0061	0.240
	13-0849	0.034	0.563	0.981	4.750	0.086	0.307	0.316	0.0044	0.214
	13-0850	0.044	0.506	0.892	4.905	0.076	0.330	0.240	0.0061	0.315
Mean		0.0381	0.5126	0.9347	4.8716	0.0782	0.3031	0.2406	0.0069	0.2697
SD		0.0052	0.0575	0.1091	0.7602	0.0112	0.0458	0.0912	0.0017	0.0643
318 mg/kg-day	13-0795	0.067	0.544	1.174	5.080	0.068	0.317	0.208	0.0079	0.371
	13-0796	0.047	0.468	0.813	4.546	0.082	0.249	0.095		0.882
	13-0805	0.053	0.390	0.899	4.828	0.064	0.140	0.088	0.0049	0.161
	13-0806	0.048	0.438	0.782	5.005	0.071	0.204	0.153	0.0062	0.211
	13-0813	0.052	0.492	0.900	5.385	0.059	0.230	0.188	0.0023	0.349
	13-0814	0.040	0.406	0.813	4.919	0.060	0.265	0.171	0.0076	0.180
	13-0825	0.037	0.511	0.814	4.631	0.054	0.190	0.078	0.0054	0.230
	13-0826	0.044	0.437	0.821	5.612	0.068	0.237	0.088	0.0093	0.140
	13-0839	0.052	0.558	0.903	4.904	0.068	0.188	0.172	0.0040	0.226
	13-0840	0.044	0.375	0.785	4.370	0.042	0.223	0.146	0.0068	0.213
Mean		0.0485	0.4618*	0.8705	4.9280	0.06367*	0.2243*	0.1386	0.0060	0.2963
SD		0.0085	0.0637	0.1167	0.3744	0.0106	0.0484	0.0476	0.0021	0.2191

*Significantly different from control

Table J-6
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Organ Mass/Brain Mass
Male Rats

ORGAN MASS/BRAIN MASS										
Group	Animal ID	adrenals	heart	kidneys	epididymi des	liver	spleen	testes	thymus	thyroid
0 mg/kg-day	13-0855	0.029	0.707	1.359	0.454	5.776	0.337	1.582	0.294	0.002
	13-0856	0.025	0.712	1.295	0.434	5.856	0.303	1.425	0.232	0.011
	13-0873	0.024	0.779	1.365	0.518	7.617		1.863	0.306	0.006
	13-0874	0.028	0.698	1.344	0.461	6.170	0.447	1.599	0.205	0.009
	13-0879	0.042	0.641	1.212	0.447	5.847	0.354	1.605	0.204	0.006
	13-0880	0.032	0.792	1.488	0.527	7.221	0.437	1.519	0.226	0.006
	13-0891	0.033	0.704	1.256	0.398	5.975	0.453	1.466	0.414	0.007
	13-0892	0.038	0.782	1.340	0.454	6.764	0.471	1.535	0.255	0.006
	13-0901	0.037	0.771	1.396	0.430	7.650	0.435	1.555	0.324	0.006
	13-0902	0.042	0.793	1.312	0.622	6.894	0.375	1.740	0.298	0.006
	Mean	0.0331	0.7378	1.3366	0.4747	6.5771	0.4013	1.5889	0.2759	0.0066
	SD	0.0066	0.0522	0.0761	0.0648	0.7457	0.0599	0.1289	0.0652	0.0023
47 mg/kg-day	13-0861	0.031	0.617	1.223	0.433	6.575	0.361	1.615	0.291	0.008
	13-0862	0.031	0.640	1.244	0.384	6.067	0.249	1.521	0.114	0.008
	13-0865	0.029	0.596	1.224	0.510	5.591	0.329	1.702	0.263	0.007
	13-0866	0.045	0.766	1.631	0.409	8.081	0.395	1.544	0.218	0.009
	13-0869	0.045	0.692	1.206	0.441	6.442	0.360	1.767	0.237	0.007
	13-0870	0.033	0.590	1.190	0.441	5.535	0.446	1.576	0.294	0.008
	13-0889	0.029	0.673	1.315	0.408	6.120	0.428	1.471	0.311	0.006
	13-0890	0.034	0.669	1.520	0.552	6.513	0.456	1.928	0.229	0.007

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	13-0911	0.028	0.676	1.414	0.518	6.825	0.481	1.525	0.271	0.006
	13-0912	0.032	0.634	1.381	0.480	6.741	0.314	1.458	0.256	0.010
	Mean	0.0337	0.6555	1.3347	0.4575	6.4490	0.3818	1.6107	0.2482	0.0076
	SD	0.0062	0.0521	0.1496	0.0549	0.7255	0.0727	0.1481	0.0558	0.0013
93 mg/kg-day	13-0859	0.037	0.614	1.202	0.404	5.994	0.316	1.481	0.195	0.007
	13-0860	0.025	0.621	1.270	0.504	6.816	0.436	1.586	0.240	0.006
	13-0875	0.037	0.658	1.380	0.482	6.324	0.288	1.567	0.147	0.008
	13-0876	0.031	0.609	1.154	0.444	5.706	0.251	1.578	0.195	0.004
	13-0881	0.028	0.616	1.211	0.451	5.156	0.307	1.499	0.247	0.009
	13-0882	0.035	0.680	1.326	0.420	5.723	0.438	1.630	0.287	0.006
	13-0899	0.034	0.755	1.393	0.486	7.501	0.529	1.504	0.282	0.008
	13-0900	0.021	0.678	1.442	0.557	6.673	0.438	1.680	0.251	0.007
	13-0909	0.028	0.729	1.459	0.570	8.186	0.438	1.729	0.253	0.006
	13-0910	0.026	0.744	1.607	0.478	6.965	0.418	1.597	0.271	0.007
	Mean	0.0302	0.6706	1.3442	0.4796	6.5042	0.3859	1.5851	0.2367	0.0068
	SD	0.0053	0.0564	0.1395	0.0540	0.9140	0.0889	0.0795	0.0447	0.0014
185 mg/kg-day	13-0867	0.030	0.532	1.018	0.457	4.912	0.292	1.673	0.204	0.005
	13-0868	0.031	0.648	1.332	0.463	7.425	0.374	1.648	0.215	0.009
	13-0877	0.037	0.512	1.107	0.405	5.818	0.330	1.450	0.074	0.005
	13-0878	0.030	0.362	1.376	0.332	3.608	0.097	1.559	0.030	0.008
	13-0883	0.046	0.536	1.182	0.365	5.921	0.274	1.389	0.177	0.005
	13-0884	0.039	0.629	1.348	0.547	5.696	0.345	1.844	0.225	0.006
	13-0897	0.023	0.715	1.385	0.438	6.089	0.338	1.552	0.148	0.008
	13-0898	0.036	0.745	1.392	0.472	8.321	0.465	1.705	0.246	0.007
	13-0903		0.435	1.107	0.497	5.172	0.300	1.643	0.171	0.006
	13-0904	0.043	0.580	1.559	0.510	6.187	0.376	1.643	0.248	0.009
	Mean	0.0350	0.5692*	1.2806	0.4488	5.9149	0.3191	1.6107	0.1738*	0.0069
	SD	0.0072	0.1196	0.1688	0.0661	1.2960	0.0949	0.1298	0.0725	0.0016

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370 mg/kg-day	13-0857	0.041	0.483	1.106	0.403	5.151	0.124	1.663	0.117	0.007
	13-0858	0.023	0.447	0.888	0.371	4.408	0.199	1.871	0.124	0.006
	13-0871									
	13-0872	0.048	0.599	1.190	0.335	5.379	0.223	1.715	0.120	0.008
	13-0893	0.038	0.480	1.052	0.427	5.129	0.186	1.846	0.104	0.007
	13-0894	0.049	0.864	1.307	0.368	6.141	0.230	1.647	0.115	0.009
	13-0895	0.044	0.796	1.112	0.363	6.677	0.199	2.003	0.067	0.007
	13-0896	0.034	0.636	1.921	0.346	8.000	0.230	1.568	0.103	0.007
	13-0905	0.032	0.572	0.992	0.334	5.739	0.162	1.858	0.096	0.008
	13-0906	0.045	0.497	1.505	0.322	6.486	0.229	1.532	0.209	0.004
Mean		0.0392	0.5971	1.2302	0.3633*	5.9012	0.1978*	1.7449	0.1171*	0.0071
SD		0.0085	0.1467	0.3153	0.0342	1.0659	0.0362	0.1579	0.0386	0.0013
741 mg/kg-day	13-0863	0.028	0.595	1.133	0.274	5.502	0.173	1.621	0.135	0.006
	13-0864	0.022	0.733	1.133	0.396	5.037	0.173	1.864	0.054	0.006
	13-0885	0.034	0.557	1.024	0.346	5.500	0.218	1.701	0.100	0.007
	13-0886									
	13-0887	0.037	0.997	1.280	0.299	6.305	0.273	1.725	0.136	0.008
	13-0888	0.035	0.764	1.140	0.320	6.018	0.244	1.784	0.120	0.006
	13-0907	0.033	0.842	0.928	0.317	4.986	0.165	1.431	0.092	0.005
	13-0908	0.037	0.584	1.092	0.316	5.725	0.198	1.581	0.125	0.011
	13-0913									
	13-0914	0.029	0.579	1.051	0.374	6.725	0.196	1.540	0.158	0.007
Mean		0.0318	0.7066	1.0976	0.3302*	5.7247	0.2050*	1.6560	0.1152*	0.0070
SD		0.0053	0.1571	0.1029	0.0398	0.6026	0.0381	0.1401	0.0323	0.0020

*Significantly different from control

Table J-7
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Organ Mass Body Mass Covariate
Female Rats

ORGAN MASS with BODY MASS COVARIATE

Group		adrenals	brain	heart	kidneys	liver	ovaries	spleen	thymus	thyroid	uterus
0 mg/kg-day	Mean	0.076	1.876	0.985	1.746	7.763	0.147	0.535	0.373	0.011	0.512
	SEM	0.003	0.027	0.024	0.04	0.212	0.006	0.022	0.033	0.001	0.071
20 mg/kg-day	Mean	0.073	1.907	0.991	1.846	7.917	0.145	0.547	0.469	0.011	0.537
	SEM	0.003	0.026	0.023	0.038	0.204	0.006	0.021	0.032	0.001	0.069
40 mg/kg-day	Mean	0.081	1.864	0.989	1.790	8.404	0.146	0.527	0.501	0.012	0.479
	SEM	0.003	0.027	0.024	0.039	0.209	0.006	0.023	0.034	0.001	0.071
80 mg/kg-day	Mean	0.078	1.924	1.029	1.789	8.739*	0.142	0.528	0.492	0.013	0.510
	SEM	0.003	0.026	0.023	0.038	0.204	0.006	0.021	0.032	0.001	0.069
159 mg/kg-day	Mean	0.072	1.886	0.971	1.773	9.276*	0.148	0.573	0.459	0.013	0.513
	SEM	0.003	0.026	0.023	0.038	0.204	0.006	0.021	0.032	0.001	0.069
318 mg/kg-day	Mean	0.093*	1.857	0.908	1.717	9.858*	0.126	0.441	0.334	0.011	0.576
	SEM	0.003	0.029	0.026	0.042	0.225	0.006	0.023	0.035	0.001	0.076

*Significantly different from control

Table J-8
Protocol No. 30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Organ Mass with Body Mass Covariate
Male Rats

ORGAN MASS with BODY MASS COVARIATE

Group		adrenals	brain	heart	kidneys	epididymides	liver	spleen	testes	thymus	thyroid
0 mg/kg-day	Mean	0.064	1.981	1.311	2.497	0.925	11.364	0.690	3.153	0.479	0.013
	SEM	0.005	0.038	0.059	0.129	0.033	0.486	0.043	0.089	0.038	0.001
47 mg/kg-day	Mean	0.064	1.947	1.166	2.488	0.882	11.381	0.659	3.137	0.429	0.015
	SEM	0.004	0.036	0.055	0.120	0.031	0.451	0.039	0.083	0.035	0.001
93 mg/kg-day	Mean	0.059	1.983	1.234	2.568	0.944	11.811	0.690	3.149	0.423	0.013
	SEM	0.004	0.035	0.054	0.117	0.030	0.442	0.038	0.081	0.035	0.001
185 mg/kg-day	Mean	0.069	1.961	1.149	2.541	0.882	11.961	0.647	3.153	0.358	0.014
	SEM	0.004	0.033	0.050	0.110	0.028	0.413	0.035	0.076	0.032	0.001
370 mg/kg-day	Mean	0.078	1.974	1.338	2.605	0.731*	13.426	0.515	3.414	0.318	0.014
	SEM	0.005	0.040	0.062	0.136	0.035	0.511	0.043	0.094	0.040	0.001
741 mg/kg-day	Mean	0.065	1.962	1.612	2.401	0.670*	13.770	0.579	3.221	0.349	0.014
	SEM	0.006	0.048	0.073	0.160	0.041	0.604	0.051	0.111	0.047	0.001

*Significantly different from control

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Appendix K

Individual and Summary of Clinical Chemistry Data

Table K-1
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Clinical Chemistry Analyses							
Female Rats							
Group	Animal ID	ALKP (U/L)	ALT (U/L)	AMYL (U/L)	TBIL (mg/dL)	CHOL (mg/dL)	GLU (mg/dL)
Control	13-0799	151	48	538	0.4	72	206
	13-0800	84	44	520	0.5	75	232
	13-0811	101	52	503	0.7	66	78
	13-0812	115	42	450	0.5	88	65
	13-0815	184	50	602	0.2	83	210
	13-0816	120	54	645	0.2	59	264
	13-0821	122	57	753	0.4	59	258
	13-0822	187	43	551	0.3	44	214
	13-0831	144	47	816	0.3	88	312
	13-0832	132	34	779	0.4	69	133
	Mean	134.0	47.1	615.7	0.39	70.3	197.2
	SD	33.3	6.7	127.5	0.15	14.1	80.9
20 mg/kg	13-0823	163	55	638	0.3	61	231
	13-0824	85	41	563	0.2	66	216
	13-0833	111	82	625	0.4	90	179
	13-0834	98	46	602	0.4	82	194
	13-0835	122	53	892	0.4	114	212
	13-0836	152	54	748	0.4	64	266
	13-0841	141	54	917	0.3	79	292
	13-0842	131	78	793	0.5	74	263

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40 mg/kg	13-0843	134	47	1423	0.3	61	306
	13-0844	130	59	742	0.3	90	216
	Mean	126.7	56.9	794.3	0.35	78.1	237.5
	SD	23.7	13.3	251.3	0.08	16.8	42.2
	13-0807	72	51	401	0.4	73	127
	13-0808	89	50	547	0.4	85	169
	13-0817	121	42	638	0.4	92	214
	13-0818	90	58	672	0.5	94	120
	13-0819	96	54	621	0.5	95	95
	13-0820	104	47	725	0.4	80	99
80 mg/kg	13-0845	92	44	864	0.4	75	311
	13-0846	109	50	821	0.4	70	309
	13-0847	137	52	1126	0.4	88	245
	13-0848	175	64	642	0.3	90	237
	Mean	108.5	51.2	705.7	0.41	84.2*	192.6
	SD	29.6	6.5	197.3	0.06	9.1	82.4
	13-0797	98	50	570	0.3	100	312
	13-0798	92	51	534	0.4	100	169
	13-0809	69	45	520	0.4	112	156
	13-0810						
	13-0827	112	33	769	0.4	109	201
	13-0828	89	50	661	0.4	67	250
	13-0851	97	40	886	0.4	101	227
	13-0852	142	50	1038	0.4	81	201
	13-0853	101	46	819	0.5	112	158
	13-0854	138	58	827	0.6	112	212
	Mean	104.2*	47.0	736.0	0.42	99.3*	209.6

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	SD	23.3	7.2	177.0	0.08	15.7	49.7
159 mg/kg	13-0801	88	54	599	0.4	115	239
	13-0802	116	37	786	0.5	111	258
	13-0803	104	47	683	0.4	84	240
	13-0804	87	47	605	0.5	104	185
	13-0829	107	55	740	0.4	82	87
	13-0830	108	52	1086	0.5	117	83
	13-0837	101	38	834	0.4	103	310
	13-0838	167	50	766	0.4	112	251
	13-0849	117	66	970	0.4	89	248
	13-0850	82	53	888	0.5	104	236
	Mean	107.7*	49.9	795.7	0.44	102.1*	213.7
	SD	24.1	8.4	155.1	0.05	12.8	74.2
318 mg/kg	13-0795	102	61	544	0.3	95	287
	13-0796	74	80	934	0.9	119	285
	13-0805	108	67	2044	0.6	138	325
	13-0806	107	53	704	0.5	137	263
	13-0813	69	50	746	0.4	112	203
	13-0814	54	69	668	0.4	105	168
	13-0825						
	13-0826	84	69	998	0.2	93	229
	13-0839	79	52	2173	0.4	99	207
	13-0840	70	52	960	0.4	113	196
	Mean	83.0*	61.4*	1085.7*	0.46	112.3*	240.3
	SD	18.9	10.4	599.6	0.20	16.7	52.1

*Significantly different from control

Table K-2
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Clinical Chemistry Analyses											
Female Rats											
Group	Animal ID	ALB (g/dL)	GLOB (mg/dL)	TP (g/dL)	BUN (mg/dL)	CREA (mg/dL)	CA (mg/dL)	PHOS (mg/dL)	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)
Control	13-0799	3.4	3.2	6.6	21	0.8	12.9	15.8	152	12.2	104
	13-0800	3.2	3.2	6.3	24	0.7	11.9	15.4	150	10.8	105
	13-0811	3.1	3.0	6.0	20	0.9	11.9	15.9	150	11.1	107
	13-0812	3.4	3.3	6.8	19	0.8	12.1	13.9	154	9.6	107
	13-0815	2.7	3.5	6.2	24	0.7	11.6	11.9	150	7.4	102
	13-0816	3.3	2.9	6.2	29	0.7	11.5	11.6	151	8.3	106
	13-0821	2.7	3.6	6.3	34	0.8	11.9	14.8	150	10.6	106
	13-0822	2.8	3.4	6.1	22	0.7	11.3	11.7	151	8.2	105
	13-0831	3.4	2.9	6.3	20	0.7	11.5	12.4	150	9.2	103
	13-0832	3.8	2.9	6.7	22	1.0	11.6	12.8	153	10.6	105
Mean		3.18	3.19	6.35	23.5	0.78	11.82	13.62	151.1	9.80	105.0
SD		0.36	0.26	0.26	4.7	0.10	0.45	1.75	1.4	1.52	1.6
20 mg/kg	13-0823	2.8	3.1	5.8	17	0.6	11.7	14.7	149	7.5	107
	13-0824	3.1	3.4	6.5	12	0.6	11.5	12.1	153	7.8	108
	13-0833	2.9	3.4	6.3	22	0.7	12.4	16.2	153	9.5	107
	13-0834	3.0	3.3	6.2	22	0.8	11.9	12.3	151	9.5	102
	13-0835	3.7	2.7	6.4	23	0.7	11.8	11.3	150	8.6	105
	13-0836	3.5	2.9	6.3	22	0.7	11.8	12.0	151	8.3	106
	13-0841	4.1	2.8	6.9	23	0.9	12.7	14.6	151	14.9	106

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40 mg/kg	13-0842	3.7	2.7	6.4	35	0.7	11.9	13.0	151	11.6	105
	13-0843	3.6	2.6	6.2	23	0.7	12.1	12.2	152	9.3	106
	13-0844	3.2	3.0	6.2	29	0.6	11.3	12.6	151	8.2	104
	Mean	3.36	2.99	6.32	22.8	0.70	11.91	13.10	151.2	9.52	105.6
	SD	0.42	0.30	0.28	6.1	0.09	0.41	1.55	1.2	2.22	1.7
	13-0807	3.5	2.9	6.4	26	0.6	11.5	11.2	150	7.0	107
	13-0808	2.8	3.3	6.1	28	0.6	11.2	12.6	150	6.7	107
	13-0817	3.4	3.1	6.5	16	0.6	11.9	13.5	152	8.3	104
	13-0818	3.8	3.5	7.3	34	0.8	12.2	15.3	152	11.0	105
	13-0819	3.6	3.7	7.3	20	0.9	12.0	13.9	155	9.6	106
	13-0820	3.3	3.7	7.0	19	0.9	11.8	13.5	155	10.0	107
	13-0845	3.8	2.8	6.6	23	0.8	12.2	14.0	151	9.8	104
	13-0846	3.8	2.9	6.7	34	0.7	12.3	13.0	150	12.8	107
	13-0847	3.3	3.0	6.3	27	0.8	11.3	12.3	153	10.1	106
	13-0848	3.2	2.7	5.8	33	0.7	11.2	13.9	151	10.4	107
	Mean	3.45	3.16	6.60	26.0	0.74	11.76	13.32	151.9	9.57	106.0
	SD	0.32	0.37	0.49	6.5	0.12	0.43	1.12	1.9	1.83	1.2
80 mg/kg	13-0797	3.1	3.5	6.7	15	0.8	11.7	14.7	151	11.0	102
	13-0798	3.4	3.3	6.7	20	0.7	11.7	13.8	151	7.7	102
	13-0809	3.4	3.2	6.6	18	0.6	11.7	9.7	153	6.2	103
	13-0810										
	13-0827	3.7	3.2	6.9	19	0.8	11.7	12.4	152	10.1	105
	13-0828	3.8	3.2	7.0	33	0.7	11.7	12.9	151	9.5	106
	13-0851	3.8	2.8	6.6	11	0.6	11.8	11.9	152	9.0	104
	13-0852	3.4	2.9	6.3	18	0.7	11.5	13.6	152	7.8	105
	13-0853	3.3	3.3	6.5	15	0.7	11.3	12.2	150	7.6	106
	13-0854	3.2	3.3	6.5	21	0.7	11.3	11.8	152	8.3	105

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159 mg/kg	Mean	3.46	3.19	6.64	18.9	0.70	11.60	12.56	151.6	8.58	104.2
	SD	0.26	0.21	0.21	6.1	0.07	0.19	1.44	0.9	1.47	1.6
	13-0801	3.7	3.0	6.7	21	0.5	12.6	13.4	151	10.2	105
	13-0802	3.6	3.4	7.0	21	0.5	12.2	13.0	153	12.0	105
	13-0803	3.5	3.0	6.5	21	0.6	11.5	13.9	152	10.5	107
	13-0804	3.6	3.0	6.6	21	0.7	11.6	12.3	153	9.0	105
	13-0829	3.1	3.1	6.3	25	0.6	10.5	10.2	152	8.1	106
	13-0830	3.9	3.0	6.9	23	0.7	11.0	11.5	153	9.8	106
	13-0837	3.5	3.1	6.6	17	0.6	11.8	13.0	151	8.9	105
	13-0838	3.4	2.9	6.2	25	0.7	11.4	11.3	151	8.9	106
318 mg/kg	13-0849	3.6	2.8	6.4	27	0.9	12.0	12.5	151	11.1	105
	13-0850	3.4	2.9	6.3	20	0.8	11.6	12.5	152	9.4	106
	Mean	3.53	3.02	6.55	22.1	0.66	11.62	12.36	151.9	9.79	105.6
	SD	0.21	0.16	0.26	2.9	0.13	0.59	1.10	0.9	1.18	0.7
	13-0795	2.9	3.2	6.1	22	0.8	12.1	14.2	151	10.1	105
	13-0796	3.0	3.3	6.3	30	0.6	11.1	10.2	148	7.6	99
	13-0805	3.1	3.7	6.9	84	0.9	12.0	15.1	146	7.1	90
	13-0806	3.2	3.4	6.7	26	0.7	12.4	13.8	155	9.4	101
	13-0813	4.2	3.3	7.5	17	0.6	12.2	13.5	150	8.5	103
	13-0814	2.8	3.7	6.5	19	0.6	11.7	12.1	149	9.0	102
	13-0825										
	13-0826	2.6	3.0	5.4	20	0.5	10.9	11.3	149	8.1	104
	13-0839	3.3	3.3	6.6	26	0.6	11.7	13.8	154	9.6	103
	13-0840	3.8	3.1	6.9	15	0.6	11.1	9.4			
	Mean	3.21	3.33	6.54	28.8	0.66	11.69	12.60	150.3	8.68	100.9*
	SD	0.50	0.24	0.59	21.3	0.12	0.54	1.95	3.0	1.04	4.8

*Significantly different from control

Table K-3
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Clinical Chemistry Analyses							
Male Rats							
Group	Animal ID	ALKP (U/L)	ALT (U/L)	AMYL (U/L)	TBIL (mg/dL)	CHOL (mg/dL)	GLU (mg/dL)
Control	13-0855	285	65	1247	0.4	93	139
	13-0856	313	44	1334	0.4	43	461
	13-0873	148	131	1345	0.5	67	72
	13-0874	234	60	789	0.4	59	97
	13-0879	159	40	986	0.2	33	88
	13-0880	188	57	1121	0.3	76	83
	13-0891	224	45	1167	0.3	72	273
	13-0892	229	52	1099	0.3	83	422
	13-0901	230	46	1290	0.3	78	233
	13-0902	178	72	1156	0.4	56	339
	Mean	218.8	61.2	1153.4	0.35	66.0	220.7
	SD	52.6	26.6	170.5	0.08	18.5	147.5
47 mg/kg	13-0861	227	37	926	0.4	92	277
	13-0862	222	40	1331	0.3	79	342
	13-0865	221	42	932	0.2	72	100
	13-0866	138	53	1091	0.3	66	107
	13-0869	190	49	1118	0.4	105	129
	13-0870	171	67	1019	0.3	62	121
	13-0889						
	13-0890	251	69	1009	0.1	94	185

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	13-0911	189	41	983	0.4	97	274
	13-0912	207	52	1431	0.5	109	344
	Mean	201.8	50.0	1093.3	0.32	86.2*	208.8
	SD	33.9	11.6	176.8	0.12	17.1	101.1
93 mg/kg	13-0859	233	50	1187	0.3	79	265
	13-0860	202	59	1275	0.4	83	218
	13-0875	205	69	1226	0.3	83	192
	13-0876	174	58	1220	0.5	108	140
	13-0881	134	74	1141	0.3	86	180
	13-0882	184	58	887	0.3	94	88
	13-0899	193	68	1001	0.3	121	149
	13-0900	129	138	1265	0.7	67	348
	13-0909	210	70	1050	0.3	113	431
	13-0910	187	58	1092	0.3	81	244
	Mean	185.1	70.2	1134.4	0.37	91.5*	225.5
	SD	32.6	24.9	126.2	0.13	17.2	102.4
185 mg/kg	13-0867	173	76	755	0.3	121	191
	13-0868	209	68	781	0.3	95	213
	13-0877	151	59	916	0.5	128	98
	13-0878	135	54	1789	0.5	93	272
	13-0883	130	58	654	0.4	122	253
	13-0884	134	62	684	0.2	82	120
	13-0897	126	89	989	0.6	83	363
	13-0898	199	49	930	0.3	102	126
	13-0903	154	102	827	0.3	118	333
	13-0904	187	61	1015	0.2	101	355
	Mean	159.8*	67.8	934.0*	0.36	104.5*	232.4

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	SD	30.4	16.6	324.7	0.13	16.7	99.1
370 mg/kg	13-0857	247	75	2448	0.6	154	236
	13-0858	122	60	773	0.2	75	227
	13-0871						
	13-0872	155	59	718	0.4	139	258
	13-0893	195	136	732	0.3	136	185
	13-0894						
	13-0895	190	59	1609	1.0	200	227
	13-0896	366	76	1920	0.4	152	318
	13-0905	157	84	874	0.5	143	527
	13-0906	141		654	3.5	50	95
	Mean	196.6	78.4*	1216.0	0.86	131.1*	259.1
	SD	78.6	27.3	684.4	1.09	47.3	125.5
741 mg/kg	13-0863	352	100	2086	0.7	137	282
	13-0864						
	13-0885	303	62	1034	0.5	145	354
	13-0886						
	13-0887						
	13-0888	188	40	1144	0.6	136	557
	13-0907						
	13-0908	336	37	1176	0.3	125	326
	13-0913						
	13-0914	333	61	2022	0.3	169	624
	Mean	302.4*	60.0	1492.4	0.48	142.4*	428.6*
	SD	66.4	25.2	515.9	0.18	16.5	151.9

*Significantly different from control

Table K-4
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Clinical Chemistry Analyses											
Male Rats											
Group	Animal ID	ALB (g/dL)	GLOB (mg/dL)	TP (g/dL)	BUN (mg/dL)	CREA (mg/dL)	CA (mg/dL)	PHOS (mg/dL)	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)
Control	13-0855	3.3	3.1	6.4	27	0.9	11.8	14.6	155	11.3	108
	13-0856	3.4	2.9	6.4	10	0.8	12.9	14.8	152	12.7	107
	13-0873	3.2	3.2	6.4	23	0.8	11.3	14.8	150	11.7	106
	13-0874	3.2	3.1	6.3	18	0.9	11.4	13.0	152	10.7	105
	13-0879	2.9	3.1	6.0	14	0.6	11.9	15.5	153	9.9	105
	13-0880	3.0	3.2	6.2	11	0.5	11.6	13.9	154	9.5	106
	13-0891	3.4	2.9	6.2	11	0.7	12.1	15.6	155	11.1	106
	13-0892	3.2	3.0	6.2	22	0.6	12.4	14.9	153	10.9	105
	13-0901	3.3	3.0	6.3	14	0.6	11.8	13.3	153	9.4	102
	13-0902	3.3	3.2	6.5	16	0.7	11.7	14.0	152	11.3	102
Mean		3.22	3.07	6.29	16.6	0.71	11.89	14.44	152.9	10.85	105.2
SD		0.16	0.12	0.14	5.8	0.14	0.48	0.87	1.5	1.03	1.9
47 mg/kg	13-0861	2.9	3.0	5.9	13	0.8	11.7	14.5	154	9.9	106
	13-0862	2.9	3.1	6.0	14	0.8	12.0	13.4	153	10.0	106
	13-0865	2.8	3.2	6.0	19	0.7	11.1	13.9	152	8.0	106
	13-0866	3.0	3.3	6.3	13	0.7	11.3	15.8	154	10.2	106
	13-0869	3.0	3.1	6.1	17	0.5	11.4	15.0	155	9.9	107
	13-0870	2.9	3.1	6.0	11	0.7	11.3	11.1	154	8.1	107
	13-0889										
	13-0890	2.9	3.0	6.0	19	0.6	11.0	12.7	154	8.4	104

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93 mg/kg	13-0911	3.0	3.2	6.2	15	0.4	11.3	10.1	149	6.5	102
	13-0912	3.5	2.9	6.4	13	0.5	12.1	12.5			
	Mean	2.99*	3.10	6.10	14.9	0.63	11.47	13.22	153.1	8.88*	105.5
	SD	0.20	0.12	0.17	2.8	0.14	0.38	1.84	1.9	1.33	1.7
	13-0859	2.7	2.9	5.6	20	0.7	11.1	12.2	151	7.4	108
	13-0860	2.8	3.0	5.9	19	0.6	11.0	11.4	154	8.9	106
	13-0875	2.7	3.1	5.8	14	0.7	11.5	15.4	155	10.5	107
	13-0876	3.0	3.3	6.3	12	0.6	11.9	14.8	154	11.9	108
	13-0881	3.2	2.9	6.0	12	0.4	11.7	12.3	153	8.1	107
	13-0882	3.2	2.9	6.2	11	0.4	11.5	11.8	155	8.3	106
185 mg/kg	13-0899	3.1	2.9	6.1	11	0.4	11.0	12.6	155	8.9	105
	13-0900	3.7	1.9	5.6	14	0.5	11.5	22.3	150	11.1	105
	13-0909	2.9	2.9	5.8	18	0.6	11.5	13.9	151	10.8	105
	13-0910	3.1	2.7	5.8	20	0.7	11.5	14.7	151	12.1	106
	Mean	3.04*	2.85	5.91	15.1	0.56	11.42	14.14	152.9	9.80	106.3
	SD	0.30	0.37	0.24	3.8	0.13	0.30	3.19	2.0	1.68	1.2
	13-0867	2.6	3.1	5.7	14	0.7	11.1	12.1	151	8.6	104
	13-0868	2.5	2.9	5.4	16	0.6	10.9	10.7	152	7.9	108
	13-0877	2.9	3.5	6.4	10	0.5	11.1	9.7	153	6.4	101
	13-0878	2.6	2.9	5.5	11	0.9	10.6	13.7	138	6.6	91
	13-0883	3.2	3.0	6.3	16	0.6	11.6	14.3	151	11.2	104
	13-0884	2.4	3.0	5.5	11	0.6	11.0	11.1	153	8.5	107
	13-0897	2.9	3.0	5.9	13	0.6	11.8	17.1			
	13-0898	2.9	3.0	5.9	11	0.7	11.0	12.9	155	8.3	105
	13-0903	2.8	3.2	5.9	18	0.5	11.3	10.9	153	8.4	106
	13-0904	3.0	2.7	5.7	10	0.5	11.9	13.2	154	10.7	107
	Mean	2.78*	3.03	5.82	23.0	0.62	11.23	12.57	151.1	8.51*	103.7

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	SD	0.25	0.21	0.33	31.0	0.12	0.42	2.17	5.1	1.60	5.2
370 mg/kg	13-0857	3.8	3.9	7.8	122	1.5	12.1	16.1			
	13-0858	2.2	3.1	5.3	27	0.6	10.9	11.7	143	8.3	98
	13-0871										
	13-0872	2.7	3.8	6.5	27	0.8	12.0	15.9	153	9.9	103
	13-0893	2.3	3.2	5.6	92	1.6	11.3	16.0	148	7.9	98
	13-0894										
	13-0895	3.9	3.8	7.7	96	1.2	11.8	16.1			
	13-0896	2.8	3.6	6.4	130	2.0	8.3	16.1	149	6.7	96
	13-0905	3.5	3.0	6.5	57	0.8	11.8	16.1	143	8.2	85
	13-0906	1.9	2.7	4.6	130		7.2	16.1	137	10.2	96
	Mean	2.89	3.39	6.30	85.1*	1.21*	10.68	15.51*	145.5*	8.53*	96.0*
	SD	0.76	0.45	1.11	43.3	0.51	1.87	1.54	5.6	1.31	6.0
741 mg/kg	13-0863	3.1	3.2	6.3	69	0.7	11.4	15.2	148	7.4	101
	13-0864										
	13-0885	2.7	3.1	5.8	22	0.5	11.5	12.7	148	8.6	101
	13-0886										
	13-0887										
	13-0888	2.7	3.2	5.9	18	0.7	11.6	15.5	146	10.0	96
	13-0907										
	13-0908	2.6	3.3	5.9	26	0.6	11.7	15.2	153	8.9	99
	13-0913										
	13-0914	2.6	3.4	6.0	45	1.2	12.3	15.9			
	Mean	2.74*	3.24*	5.98	36.0*	0.74	11.70	14.90	148.8*	8.73*	99.3*
	SD	0.21	0.11	0.19	21.2	0.27	0.35	1.26	3.0	1.07	2.4

*Significantly different from control

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Appendix L

Individual and Summary of Hematology Data

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Table L-1
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Hematology Analyses												
Female Rats												
Group	Animal ID	WBC (K/uL)	NEU (K/uL)	(%N)	LYM (K/uL)	(%L)	MONO (K/uL)	(%M)	EOS (K/uL)	(%E)	BASO (K/uL)	(%B)
Control	13-0799	11.60	1.780	15.300	9.580	82.400	0.037	0.316	0.128	1.100	0.101	0.873
	13-0800	14.70	0.859	5.850	12.600	85.600	0.587	4.000	0.078	0.531	0.593	4.040
	13-0811											
	13-0812	8.34	0.428	5.130	7.000	83.900	0.446	5.350	0.067	0.799	0.404	4.850
	13-0815	13.60	1.560	11.400	11.100	81.000	0.679	4.980	0.091	0.664	0.271	1.980
	13-0816	10.60	1.880	17.700	7.600	71.400	0.505	4.750	0.080	0.748	0.578	5.430
	13-0821	11.00	2.190	19.800	7.510	68.100	0.679	6.150	0.089	0.802	0.571	5.170
	13-0822	9.86	1.520	15.400	7.550	76.600	0.365	3.710	0.102	1.030	0.320	3.250
	13-0831	9.39	1.750	18.600	6.560	69.800	0.628	6.680	0.100	1.070	0.364	3.880
	13-0832	7.64	1.130	14.800	5.280	69.200	0.779	10.200	0.038	0.500	0.404	5.290
	Mean	10.748	1.4552	13.7756	8.3089	76.4444	0.5228	5.1262	0.0859	0.8049	0.4007	3.8626
	SD	2.309	0.5528	5.2937	2.3314	6.9585	0.2227	2.6418	0.0250	0.2234	0.1628	1.5838
20 mg/kg	13-0823	14.40	1.390	9.660	12.700	88.700	0.048	0.333	0.149	1.040	0.039	0.275
	13-0824	8.55	1.140	13.400	7.120	83.300	0.045	0.530	0.169	1.980	0.074	0.869
	13-0833	14.70	0.955	6.500	13.200	89.900	0.158	1.070	0.099	0.676	0.265	1.800
	13-0834	11.40	1.060	9.310	9.320	81.800	0.579	5.080	0.167	1.470	0.266	2.340
	13-0835	8.61	0.953	11.100	6.740	78.300	0.505	5.870	0.110	1.280	0.297	3.460
	13-0836	8.91	1.070	12.100	6.930	77.700	0.548	6.150	0.080	0.898	0.282	3.170
	13-0841	12.60	1.180	9.400	10.300	81.700	0.556	4.430	0.096	0.766	0.460	3.660
	13-0842	14.30	1.950	13.600	12.000	83.800	0.103	0.715	0.146	1.020	0.124	0.863
	13-0843	13.60	0.764	5.600	11.700	85.800	0.533	3.920	0.138	1.020	0.506	3.710
	13-0844	7.38	0.636	8.620	6.450	87.400	0.056	0.765	0.022	0.297	0.217	2.930
	Mean	11.445	1.1098	9.9290	9.6460	83.8400	0.3131	2.8863	0.1176	1.0447	0.2530	2.3077
	SD	2.845	0.3632	2.6782	2.6806	4.1404	0.2464	2.4130	0.0456	0.4603	0.1512	1.2824
40 mg/kg	13-0807	11.10	0.942	8.480	8.820	8000	0.643	5.790	0.179	1.610	0.518	4.660
	13-0808	13.50	2.160	16.000	9.560	70.900	0.808	5.990	0.179	1.330	0.767	5.690
	13-0817	10.10	0.987	9.750	8.910	88.100	0.113	1.110	0.079	0.781	0.029	0.287
	13-0818	8.83	0.962	10.900	6.880	77.900	0.741	8.390	0.082	0.932	0.171	1.930
	13-0819											
	13-0820	7.21	1.190	16.600	4.660	64.700	0.564	7.820	0.065	0.896	0.724	10.000
	13-0845	13.30	1.530	11.500	10.300	77.700	0.805	6.060	0.195	1.470	0.434	3.260
	13-0846	9.65	0.765	7.930	7.550	78.300	0.590	6.110	0.111	1.150	0.633	6.560
	13-0847	8.77	1.280	14.600	6.600	75.300	0.484	5.520	0.133	1.510	0.275	3.130
	13-0848	8.70	1.200	13.700	6.020	69.200	0.591	6.790	0.217	2.490	0.678	7.790

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	Mean	10.129	1.2240	12.1622	7.7000	75.7333	0.5932	5.9533	0.1378	1.3521*	0.4699	4.8119
	SD	2.142	0.4168	3.2026	1.8340	6.8029	0.2118	2.0564	0.0565	0.5187	0.2617	3.0342
80 mg/kg	13-0797	8.50	0.690	8.120	6.660	78.300	0.608	7.150	0.124	1.460	0.420	4.930
	13-0798	12.20	1.470	12.100	9.290	76.000	0.561	4.590	0.197	1.610	0.697	5.710
	13-0809	8.48	0.846	9.980	7.090	83.600	0.249	2.940	0.037	0.435	0.257	3.030
	13-0810	9.05	1.030	11.300	7.710	85.200	0.071	0.789	0.136	1.500	0.111	1.230
	13-0827	13.40	0.810	6.040	11.100	82.800	0.801	5.970	0.120	0.895	0.574	4.280
	13-0828	18.40	1.390	7.550	15.600	84.900	0.676	3.670	0.171	0.930	0.542	2.940
	13-0851	16.60	1.030	6.180	14.600	87.800	0.543	3.270	0.145	0.872	0.310	1.870
	13-0852	7.23	0.580	8.130	6.130	84.800	0.201	2.780	0.054	0.747	0.255	3.530
	13-0853	6.61	1.230	18.600	4.720	71.400	0.364	5.510	0.093	1.400	0.207	3.120
	13-0854	10.30	0.995	9.650	8.350	81.000	0.324	3.140	0.173	1.670	0.472	4.580
	Mean	11.077	1.0071	9.7650	9.1250	81.5800	0.4398	3.9809	0.1250	1.1519	0.3845	3.5220
	SD	3.995	0.2905	3.6959	3.6059	4.9957	0.2330	1.8479	0.0516	0.4252	0.1862	1.3820
159 mg/kg	13-0801	12.80	1.560	12.200	9.930	77.600	0.575	4.490	0.151	1.180	0.590	4.600
	13-0802	11.00	3.250	29.500	5.220	47.300	1.340	12.200	0.096	0.870	1.130	10.200
	13-0803	8.10	0.604	7.460	6.740	83.200	0.329	4.060	0.450	0.554	0.378	4.670
	13-0804	11.70	2.750	23.500	7.540	64.500	0.779	6.670	0.072	0.614	0.541	4.630
	13-0829	6.05	0.786	13.000	4.640	76.800	0.284	4.690	0.041	0.675	0.294	4.860
	13-0830	6.89	1.300	18.900	4.400	63.900	0.537	7.800	0.060	0.870	0.588	8.540
	13-0837	12.50	2.180	17.500	9.130	73.300	0.481	3.860	0.147	1.180	0.517	4.150
	13-0838	8.17	1.550	18.900	5.690	69.600	0.411	5.030	0.101	1.240	0.424	5.190
	13-0849	9.95	0.991	9.950	8.150	81.900	0.374	3.760	0.079	0.792	0.360	3.620
	13-0850	8.17	1.110	13.600	6.270	76.800	0.349	4.270	0.091	1.110	0.346	4.240
	Mean	9.533	1.6081	16.4510	6.7710	71.4900	0.5459	5.6830	0.1288	0.9085	0.5168	5.4700
	SD	2.389	0.8654	6.6187	1.8864	10.7377	0.3149	2.6334	0.1180	0.2542	0.2400	2.1351
318 mg/kg	13-0795	9.99	3.100	31.100	5.760	57.700	0.582	5.830	0.077	0.770	0.466	4.660
	13-0796	15.00	10.400	69.400	2.920	19.500	1.280	8.520	0.036	0.241	0.360	2.410
	13-0805	11.90	10.900	91.600	0.857	7.190	0.097	0.811	0.011	0.090	0.036	0.300
	13-0806	9.06	7.010	77.400	1.820	20.100	0.169	1.860	0.024	0.270	0.035	0.386
	13-0813	11.30	9.460	83.500	1.740	15.300	0.103	0.908	0.026	0.227	0.008	0.072
	13-0814	7.43	3.520	47.300	3.220	43.300	0.416	5.600	0.035	0.469	0.245	3.300
	13-0825											
	13-0826	10.40	4.220	40.400	4.940	47.300	0.547	5.250	0.044	0.424	0.683	6.550
	13-0839	5.43	2.410	44.400	1.680	30.900	0.879	16.200	0.220	0.398	0.441	8.130
	13-0840	5.87	2.760	47.000	2.660	45.300	0.212	3.620	0.029	0.487	0.211	3.600
	Mean	9.598	5.9756*	59.1222*	2.8441*	31.8433*	0.4761	5.3999	0.0559*	0.3751*	0.2761	3.2676
	SD	3.050	3.4905	21.5871	1.6065	17.2932	0.3993	4.7901	0.0642	0.1976	0.2315	2.8400

*Significantly different from control

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Table L-2
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Hematology Analyses											
Female Rats											
Group	Animal ID	RBC (M/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)	PLT (K/uL)	MPV (fL)	PT (sec)
Control	13-0799	8.05	16.30	44.1	54.8	20.2	36.9	16.2	1269.0	5.85	8.65
	13-0800	7.66	15.80	42.8	55.8	20.7	37.0	14.9	1163.0	6.43	
	13-0811										
	13-0812	8.08	16.10	44.0	54.5	20.0	36.7	15.4	1367.0	5.09	8.35
	13-0815	6.89	14.60	38.2	55.4	21.1	38.2	15.9	1284.0	5.63	9.35
	13-0816	7.21	14.60	39.6	54.9	20.3	36.9	14.7	960.0	5.89	8.95
	13-0821	7.04	15.00	39.6	56.3	21.3	37.7	14.8	1099.0	5.43	9.30
	13-0822	7.01	13.90	38.0	54.3	19.9	36.6	13.9	1391.0	5.20	9.50
	13-0831	6.73	14.20	37.5	55.7	21.2	38.0	14.6	1028.0	5.70	9.05
	13-0832	7.59	16.30	43.7	57.6	21.5	37.3	15.2	1236.0	4.96	9.05
	Mean	7.362	15.200	40.83	55.48	20.69	37.26	15.07	1199.67	5.576	9.025
	SD	0.500	0.938	2.78	1.03	0.61	0.58	0.70	148.42	0.461	0.380
20 mg/kg	13-0823	6.76	14.40	38.1	56.4	21.3	37.8	14.3	1051.0	5.69	7.90
	13-0824	6.42	14.10	36.9	57.5	22.0	38.3	15.2	1129.0	5.68	8.20
	13-0833	6.92	15.50	39.7	57.3	22.3	39.0	15.1	1464.0	5.56	8.15
	13-0834	6.66	15.10	38.8	58.3	22.7	38.9	15.3	1232.0	5.34	8.05
	13-0835	7.24	14.40	38.7	53.5	19.9	37.2	14.6	1121.0	4.29	8.90
	13-0836	6.90	14.40	38.7	56.1	20.9	37.2	14.1	1274.0	5.51	9.05
	13-0841	7.67	15.90	42.2	55.1	20.7	37.5	15.2	1327.0	5.02	8.45
	13-0842	6.89	14.50	39.1	56.7	21.0	37.0	15.5	1047.0	6.06	8.95
	13-0843	7.96	15.60	43.0	54.0	19.6	36.2	13.9	1114.0	5.79	9.30
	13-0844	6.73	14.30	38.3	57.1	21.2	37.1	15.2	1116.0	5.11	9.15
	Mean	7.015	14.820	39.35	56.20	21.16	37.62	14.84	1187.50	5.405	8.610
	SD	0.476	0.644	1.87	1.55	0.98	0.89	0.57	134.21	0.500	0.515
40 mg/kg	13-0807	7.25	14.90	40.7	56.2	20.6	36.6	14.3	1230.0	5.72	10.70
	13-0808	6.55	14.05	38.6	58.9	22.1	37.5	14.9	1511.0	4.88	8.45
	13-0817	6.17	14.30	36.5	59.2	23.2	39.2	14.5	1414.0	5.61	8.30
	13-0818	6.84	15.40	39.9	58.3	22.5	38.5	14.6	1280.0	6.34	8.10
	13-0819										13.55
	13-0820	8.99	18.60	49.7	55.3	20.7	37.4	15.8	1242.0	6.74	11.25
	13-0845	6.83	14.50	38.3	56.0	21.3	38.0	14.9	1392.0	5.65	8.45
	13-0846	6.87	14.50	38.7	56.4	21.2	37.5	15.0	1249.0	5.24	8.50
	13-0847	7.38	15.00	40.8	55.2	20.3	36.8	14.8	1176.0	5.22	8.90
	13-0848	7.88	15.60	42.1	53.5	19.8	37.0	14.0	1180.0	4.80	9.90
	Mean	7.196	15.206	40.59	56.56	21.30	37.61	14.76	1297.11	5.578	9.610

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	SD	0.834	1.369	3.80	1.90	1.11	0.84	0.51	115.62	0.641	1.761
80 mg/kg	13-0797	7.72	15.70	43.3	56.0	20.3	36.2	15.8	1275.0	5.32	9.15
	13-0798	6.94	14.00	37.4	53.9	20.2	37.4	14.3	1325.0	5.39	8.90
	13-0809	6.50	14.60	38.9	59.8	22.4	37.5	15.2	1212.0	4.91	8.25
	13-0810	7.00	14.40	38.7	55.4	20.6	37.3	15.6	1269.0	5.70	7.60
	13-0827	7.89	16.60	44.9	56.9	21.0	36.9	16.8	1293.0	5.74	8.45
	13-0828	6.92	14.20	38.3	55.4	20.6	37.1	15.2	1099.0	5.74	8.45
	13-0851	6.55	14.20	37.0	56.5	21.6	38.2	14.9	1105.0	5.45	9.00
	13-0852	6.83	14.10	37.6	55.1	20.6	37.4	15.5	978.0	4.86	8.50
	13-0853	7.23	15.40	40.8	56.4	21.3	37.7	14.5	1273.0	4.68	8.75
	13-0854	6.88	14.40	38.7	56.2	21.0	37.3	15.1	1286.0	4.49	7.95
	Mean	7.046	14.760	39.56	56.16	20.96	37.30	15.29	1211.50	5.228	8.500
	SD	0.453	0.857	2.64	1.54	0.67	0.52	0.71	112.90	0.461	0.480
159 mg/kg	13-0801	6.59	13.70	36.8	55.9	20.8	37.3	14.2	1349.0	5.67	8.50
	13-0802	7.22	15.50	41.0	56.8	21.4	37.7	15.8	1331.0	5.26	8.25
	13-0803	7.02	14.20	39.1	55.7	20.2	36.3	14.8	1303.0	5.01	8.75
	13-0804	6.72	13.80	36.9	54.9	20.6	37.5	16.1	1279.0	5.16	8.55
	13-0829	7.33	14.40	38.9	53.0	19.6	37.0	14.9	1412.0	4.97	8.45
	13-0830	8.07	15.90	43.1	53.4	19.7	36.9	15.9	1290.0	5.32	8.55
	13-0837	6.31	13.50	36.1	57.3	21.3	37.2	14.9	1338.0	4.99	8.60
	13-0838	6.52	14.20	38.1	58.5	21.7	37.1	14.6	1207.0	4.94	8.70
	13-0849	6.27	13.50	36.3	58.0	21.6	37.2	15.8	1641.0	4.72	8.80
	13-0850	6.88	14.00	37.7	54.8	20.4	37.2	15.1	1468.0	4.97	8.40
	Mean	6.893	14.270	38.40	55.83	20.73	37.14	15.21	1361.80	5.101	8.555
	SD	0.547	0.817	2.23	1.85	0.76	0.37	0.64	121.50	0.264	0.167
318 mg/kg	13-0795	6.11	12.30	33.2	54.4	20.1	37.0	17.0	1543.0	5.42	9.00
	13-0796	5.59	10.70	29.6	53.0	19.1	36.1	16.1	1291.0	5.24	
	13-0805	8.22	16.30	43.7	53.2	19.9	37.3	16.5	940.0	6.05	
	13-0806	7.31	15.20	40.2	55.1	20.9	37.9	17.5	1150.0	5.62	
	13-0813	7.13	14.40	37.8	53.1	20.1	37.9	17.0	1321.0	5.64	8.00
	13-0814	6.83	14.50	38.6	56.5	21.2	37.5	16.8	1477.0	5.04	8.25
	13-0825										
	13-0826	5.54	11.40	30.8	55.5	20.6	37.1	15.6	1527.0	4.47	
	13-0839	7.47	16.10	42.0	56.3	21.6	38.4	18.3	1636.0	5.50	8.15
	13-0840	6.37	12.40	32.7	51.3	19.4	37.9	16.4	1577.0	5.75	8.35
	Mean	6.730	13.700	36.51	54.27	20.32	37.46	16.80*	1384.67	5.414	8.350
	SD	0.902	2.057	5.09	1.74	0.82	0.68	0.79	229.03	0.458	0.386

***Significantly different from control**

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Table L-3
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Hematology Analyses												
Male Rats												
Group	Animal ID	WBC (K/uL)	NEU (K/uL)	(%N)	LYM (K/uL)	(%L)	MONO (K/uL)	(%M)	EOS (K/uL)	(%E)	BASO (K/uL)	(%B)
Control	13-0855	16.50	2.300	13.900	12.600	76.200	0.734	4.460	0.035	0.211	0.850	5.160
	13-0856	12.70	1.580	12.500	9.690	76.600	0.755	5.970	0.060	0.518	0.566	4.470
	13-0873	13.00	2.450	18.800	8.570	66.000	0.829	6.380	0.109	0.838	1.040	7.980
	13-0874	10.70	1.520	14.200	8.060	75.200	0.569	5.310	0.078	0.727	0.492	4.590
	13-0879	12.90	1.620	12.500	9.850	76.200	0.593	4.590	0.033	0.254	0.840	6.490
	13-0880	8.80	1.050	12.000	6.420	72.900	0.586	6.660	0.044	0.502	0.698	7.930
	13-0891	11.90	2.200	18.500	8.620	72.500	0.524	4.410	0.061	0.510	0.480	4.040
	13-0892	11.60	1.610	13.800	8.820	75.800	0.484	4.160	0.114	0.977	0.613	5.270
	13-0901	9.17	1.860	20.300	6.390	69.600	0.435	4.740	0.045	0.486	0.440	4.790
	13-0902	9.57	1.350	14.100	6.920	72.300	0.584	6.100	0.117	1.220	0.603	6.300
	Mean	11.684	1.7540	15.0600	8.5940	73.3300	0.6093	5.2780	0.0696	0.6243	0.6622	5.7020
	SD	2.299	0.4441	2.9878	1.8723	3.4374	0.1254	0.9259	0.0330	0.3166	0.1937	1.4127
47 mg/kg	13-0861	11.70	1.170	9.970	9.360	79.700	0.533	4.540	0.065	0.554	0.610	5.200
	13-0862	6.50	0.818	12.600	4.900	75.300	0.276	4.250	0.013	0.194	0.498	7.650
	13-0865	8.71	1.730	19.900	6.230	71.500	0.319	3.670	0.050	0.576	0.380	4.360
	13-0866	8.50	1.290	15.100	5.990	70.400	0.660	7.760	0.060	0.708	0.509	5.990
	13-0869	12.80	2.120	16.600	8.770	68.700	0.934	7.320	0.111	0.866	0.835	6.540
	13-0870	14.80	2.440	16.500	11.100	75.200	0.434	2.940	0.120	0.810	0.669	4.530
	13-0889	9.03	2.360	26.100	5.080	56.200	0.875	9.690	0.034	0.374	0.682	7.550
	13-0890	5.29	0.941	17.800	4.010	75.800	0.119	2.250	0.033	0.632	0.188	3.560
	13-0911	17.00	1.780	10.500	13.000	76.400	1.230	7.250	0.096	0.564	0.905	5.330
	13-0912	9.50	1.600	16.800	7.690	80.900	0.052	0.549	0.108	1.130	0.057	0.597
	Mean	10.383	1.6249	16.1870	7.6130	73.0100	0.5432	5.0219	0.0690	0.6408	0.5333	5.1307
	SD	3.664	0.5699	4.7181	2.9227	7.0441	0.3805	2.8716	0.0376	0.2607	0.2681	2.0802
93 mg/kg	13-0859											
	13-0860	10.20	1.850	18.100	6.730	66.100	1.030	10.100	0.049	0.482	0.524	5.150
	13-0875	10.40	1.810	17.400	7.670	73.500	0.401	3.850	0.046	0.437	0.498	4.780
	13-0876	10.00	1.940	19.300	6.620	65.900	0.578	5.760	0.071	0.703	0.834	8.300
	13-0881	9.02	1.110	12.300	7.060	78.300	0.275	3.050	0.077	0.855	0.496	5.500
	13-0882	11.40	2.170	19.000	8.940	78.500	0.018	0.155	0.077	0.672	0.182	1.600
	13-0899	8.48	1.660	19.600	6.050	71.400	0.281	3.320	0.113	1.330	0.373	4.400
	13-0900	8.47	0.986	11.600	6.470	76.300	0.432	5.090	0.146	1.720	0.444	5.240
	13-0909	10.70	1.300	12.200	8.310	77.900	0.720	6.750	0.055	0.519	0.284	2.660
	13-0910	12.90	3.050	23.600	8.140	63.000	0.765	5.920	0.093	0.720	0.873	6.750

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185 mg/kg	Mean	10.174	1.7640	17.0111	7.3322	72.3222	0.5000	4.8883	0.0808	0.8264	0.5009	4.9311
	SD	1.432	0.6243	4.1120	0.9772	6.0201	0.3064	2.7797	0.0325	0.4284	0.2287	1.9901
	13-0867	13.70	3.350	24.500	9.100	66.400	0.508	3.710	0.060	0.438	0.677	4.940
	13-0868	10.50	2.390	22.700	7.140	67.800	0.496	4.710	0.082	0.780	0.421	4.000
	13-0877	10.00	2.270	22.600	6.530	65.100	0.530	5.290	0.085	0.848	0.614	6.120
	13-0878	13.00	10.600	81.500	1.120	8.600	0.581	4.480	0.022	0.167	0.683	5.260
	13-0883	10.70	4.480	42.000	4.660	43.700	1.110	10.500	0.023	0.220	0.377	3.530
	13-0884	11.50	3.390	29.400	7.120	61.800	0.511	4.440	0.046	0.396	0.456	3.960
	13-0897	12.80	3.410	26.700	7.770	60.800	0.839	6.560	0.092	0.721	0.670	5.240
	13-0898	3.37	0.745	22.100	2.220	65.800	0.192	5.680	0.015	0.437	0.204	6.050
370 mg/kg	13-0903	13.50	5.150	38.300	6.530	48.500	1.040	7.750	0.198	1.470	0.543	4.040
	13-0904	10.70	1.260	11.800	7.960	74.400	0.742	6.940	0.112	1.050	0.618	5.770
	Mean	10.977	3.7045*	32.1600*	6.0150*	56.2900*	0.6549	6.0060	0.0735	0.6527	0.5263	4.8910
	SD	2.994	2.7703	19.3267	2.5733	19.0757	0.2788	2.0212	0.0549	0.4037	0.1586	0.9501
	13-0857	12.10	11.200	93.100	0.783	6.490	0.028	0.234	0.017	0.138	0.001	0.011
	13-0858	18.40	12.500	67.600	4.000	21.700	1.390	7.530	0.007	0.035	0.580	3.140
	13-0871											
	13-0872	24.20	17.600	72.600	2.820	11.600	3.020	12.500	0.053	0.220	0.749	3.090
	13-0893	12.50	9.320	74.800	2.810	22.600	0.210	1.680	0.040	0.321	0.072	0.582
	13-0894											
741 mg/kg	13-0895											
	13-0896	13.20	7.090	53.800	3.110	23.600	2.300	17.400	0.041	0.313	0.646	4.900
	13-0905	16.80	15.100	89.800	1.520	9.020	0.164	0.978	0.029	0.174	0.011	0.065
	13-0906	11.10	6.860	61.900	1.790	16.100	2.230	20.200	0.094	0.844	0.110	0.990
	Mean	15.471	11.3814*	73.3714*	2.4047*	15.8729*	1.3346	8.6460	0.0401	0.2921*	0.3099	1.8254*
	SD	4.673	4.0185	14.1991	1.0931	6.9789	1.2193	8.2089	0.0284	0.2630	0.3317	1.8892
	13-0863	21.00	18.900	90.400	1.820	8.690	0.152	0.727	0.037	0.176	0.007	0.035
	13-0864											
	13-0885	16.50	11.100	67.300	1.980	12.100	2.100	12.700	0.063	0.381	1.240	7.530
	13-0886											
741 mg/kg	13-0887											
	13-0888	12.20	6.180	50.500	3.410	27.900	1.280	10.400	0.028	0.232	1.330	10.900
	13-0907											
	13-0908	7.23	2.010	27.800	3.250	45.000	1.080	14.900	0.021	0.288	0.869	12.000
	13-0913											
	13-0914	17.90	10.200	56.900	2.920	16.300	3.380	18.900	0.048	0.265	1.370	7.660
	Mean	14.966	9.6780*	58.5800*	2.6760*	21.9980*	1.5984	11.5254	0.0394	0.2684*	0.9632	7.6250
	SD	5.359	6.2923	22.9351	0.7323	14.7603	1.2132	6.8012	0.0166	0.0757	0.5701	4.6767

*Significantly different from control

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Table L-4
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Hematology Analyses											
Male Rats											
Group	Animal ID	RBC (M/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)	PLT (K/uL)	MPV (fL)	PT (sec)
Control	13-0855	7.71	16.50	45.7	59.2	21.5	36.2	17.2	1312.0	5.09	6.60
	13-0856	7.85	15.80	43.8	55.8	20.2	36.1	16.1	1174.0	5.62	6.20
	13-0873	8.11	16.10	45.0	55.4	19.8	35.8	16.1	780.0	5.10	8.70
	13-0874	8.48	16.90	47.0	55.5	20.0	36.0	16.5	1050.0	4.74	8.90
	13-0879	8.26	16.50	46.9	56.8	20.0	35.2	17.1	1058.0	4.82	9.70
	13-0880	8.06	15.80	45.2	56.1	19.6	34.6	15.5	861.0	4.78	8.50
	13-0891	8.14	16.30	44.9	55.1	20.0	36.3	16.9	1148.0	4.49	9.20
	13-0892	7.84	15.90	45.0	57.3	20.3	35.4	15.5	1293.0	6.14	8.75
	13-0901	7.55	15.60	44.6	59.0	20.6	35.0	15.3	1002.0	4.61	8.90
	13-0902	8.29	16.60	45.8	55.3	20.0	36.1	15.2	1236.0	5.02	9.35
	Mean	8.029	16.200	45.39	56.55	20.20	35.67	16.14	1091.40	5.041	8.480
	SD	0.287	0.424	0.99	1.51	0.53	0.58	0.76	176.74	0.500	1.153
47 mg/kg	13-0861	7.69	15.70	43.5	56.6	20.4	36.0	16.1	1132.0	4.98	8.10
	13-0862	6.61	15.00	41.5	62.9	22.8	36.2	17.2	1359.0	5.95	8.45
	13-0865	7.60	16.30	45.6	60.0	21.5	35.8	15.6	1183.0	5.51	9.75
	13-0866	8.28	17.30	49.3	59.6	20.9	35.0	16.4	1306.0	5.15	10.15
	13-0869	8.23	18.40	50.3	61.1	22.3	36.5	16.3	1195.0	5.17	9.20
	13-0870	7.72	15.80	43.9	56.9	20.5	36.0	15.4	1072.0	5.32	9.40
	13-0889	8.02	15.70	44.7	55.8	19.6	35.2	15.2	1054.0	4.72	9.15
	13-0890	7.75	15.60	44.4	57.3	20.1	35.1	15.1	593.0	5.22	9.55
	13-0911	7.92	16.60	45.9	57.9	20.9	36.2	15.8	1268.0	5.35	8.55
	13-0912	7.98	15.80	44.4	55.7	19.8	35.6	16.2	1012.0	5.41	8.20
	Mean	7.780	16.220	45.35	58.38	20.88	35.76	15.93	1117.40	5.278	9.050
	SD	0.469	0.991	2.65	2.42	1.05	0.52	0.64	215.86	0.327	0.694
93 mg/kg	13-0859										8.25
	13-0860	7.52	15.30	43.0	57.2	20.4	35.6	15.4	1210.0	4.72	8.10
	13-0875	8.65	17.50	49.5	57.2	20.3	35.4	16.9	1179.0	5.10	8.80
	13-0876	8.47	17.40	48.6	57.4	20.6	35.9	16.2	43.4		11.05
	13-0881	6.74	14.20	40.2	59.6	21.0	35.3	15.9	701.0	5.21	8.50
	13-0882	7.68	16.10	46.6	60.7	21.0	34.6	15.9	941.0	5.03	8.65
	13-0899	7.14	14.80	41.6	58.2	20.8	35.7	15.0	1187.0	5.24	9.55
	13-0900	7.50	14.10	39.9	53.2	18.8	35.4	14.3	1226.0	5.24	9.10
	13-0909	7.12	14.50	41.2	57.9	20.4	35.3	16.1	650.0	5.56	8.65
	13-0910	7.48	14.90	43.4	58.0	19.9	34.4	16.7	1239.0	5.32	8.85
	Mean	7.589*	15.422	43.78	57.71	20.36	35.29	15.82	930.71	5.178	8.950

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	SD	0.620	1.297	3.60	2.06	0.68	0.49	0.82	404.13	0.243	0.845
185 mg/kg	13-0867	7.45	15.00	41.0	55.0	20.1	36.4	16.8	1446.0	4.59	7.55
	13-0868	5.76	12.30	34.4	59.8	21.3	35.7	16.1	1263.0	4.88	7.75
	13-0877	7.65	14.70	40.5	53.0	19.2	36.2	17.4	530.0	5.05	8.65
	13-0878	8.19	15.60	41.5	50.7	19.0	37.5	16.5	1640.0	4.61	8.30
	13-0883	6.84	14.50	39.5	57.7	21.1	36.6	18.8	2254.0	4.84	8.40
	13-0884	7.72	15.60	43.8	56.7	20.2	35.6	16.5	1217.0	4.63	9.35
	13-0897	6.73	13.00	37.5	55.7	19.4	34.8	18.1	1412.0	5.29	9.50
	13-0898	7.29	14.80	41.1	56.4	20.2	35.9	16.3	812.0	5.19	8.95
	13-0903	7.36	15.00	40.6	55.1	20.4	37.0	16.0	386.0	4.85	
	13-0904	7.26	14.40	40.8	56.2	19.8	35.2	16.4	566.0	4.86	9.00
	Mean	7.225*	14.490*	40.07*	55.63	20.07	36.09	16.89	1152.60	4.879	8.606
	SD	0.664	1.062	2.54	2.49	0.76	0.82	0.92	582.69	0.239	0.672
	13-0857	9.67	18.70	51.2	53.0	19.3	36.4	17.5	987.0	5.41	
	13-0858	7.92	15.30	42.8	54.0	19.3	35.8	18.2	1398.0	4.76	
370 mg/kg	13-0871										
	13-0872	8.53	16.50	45.8	53.6	19.4	36.1	19.1	1005.0	5.50	
	13-0893	7.26	14.30	38.2	52.7	19.7	37.5	16.1	1406.0	4.98	
	13-0894										
	13-0895										
	13-0896	6.89	14.30	38.0	55.2	20.8	37.7	16.5	1220.0	4.73	
	13-0905	8.47	17.70	49.0	57.8	20.9	36.1	16.8	1166.0	5.64	
	13-0906	6.52	13.30	36.9	56.7	20.4	36.1	15.1	476.0	5.28	
	Mean	7.894	15.729	43.13	54.71	19.97	36.53*	17.04	1094.00	5.186	
	SD	1.095	1.978	5.72	1.93	0.71	0.75	1.34	319.40	0.364	
741 mg/kg	13-0863	8.20	16.40	42.1	51.3	20.0	39.0	18.9	1234.0	6.70	
	13-0864										
	13-0885	8.61	16.20	44.6	51.8	18.8	36.3	18.1	871.0	4.84	
	13-0886										
	13-0887										
	13-0888	8.14	16.60	43.3	53.2	20.4	38.3	18.2	1696.0	5.77	
	13-0907										
	13-0908	7.50	16.10	42.9	57.2	21.5	37.6	15.9	1366.0	5.02	
	13-0913										
	13-0914	10.90	21.00	56.2	51.7	19.3	37.4	19.7	940.0	6.87	
	Mean	8.670	17.260	45.82	53.04*	20.00	37.72*	18.16*	1221.40	5.840*	
	SD	1.308	2.100	5.87	2.43	1.04	1.01	1.42	334.77	0.932	

*Significantly different from control

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Appendix M

Individual and Summary of Thyroid Hormone Data

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Table M-1
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Individual Thyroid Hormones
Female Rats

Group	Animal ID	Total T ₄ (ug/dL)	Total T ₃ (ng/mL)	TSH (ng/mL)
Control	13-0799	2.60	0.69	2.48
	13-0800	1.90	0.55	1.15
	13-0811	3.50	0.70	3.38
	13-0812	2.80	0.64	
	13-0815	3.60	0.54	2.28
	13-0816	2.30	0.55	1.87
	13-0821	2.70	0.64	2.97
	13-0822	3.20	0.59	3.15
	13-0831	2.30	0.53	1.33
	13-0832	4.20	0.67	2.78
Mean		2.910	0.610	2.376
SD		0.706	0.066	0.788
20 mg/kg	13-0823	1.90	0.64	
	13-0824	3.40	0.64	3.03
	13-0833	3.10	0.65	1.41
	13-0834	2.40	0.70	2.08
	13-0835	4.70	0.59	6.54
	13-0836	3.40	0.59	10.91
	13-0841	4.20	0.82	3.49
	13-0842	3.60	0.69	2.78
	13-0843	3.40	0.55	2.60
	13-0844	3.20	0.64	1.56
Mean		3.330	0.651	3.823
SD		0.796	0.075	3.061
40 mg/kg	13-0807	2.60	0.53	2.85
	13-0808	2.30	0.54	1.87
	13-0817	3.90	0.60	
	13-0818	2.60	0.87	
	13-0819	4.60	0.70	4.18
	13-0820	3.00	0.59	2.40
	13-0845	4.10	0.70	3.32
	13-0846	2.50	0.57	2.40
	13-0847	4.10	0.60	3.49
	13-0848	1.60	0.52	1.33

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80 mg/kg	Mean	3.130	0.622	2.731
	SD	0.980	0.107	0.923
	13-0797	2.60	0.64	
	13-0798	2.50	0.61	
	13-0809	3.90	0.63	3.54
	13-0810	3.40	0.85	1.65
	13-0827	3.10	0.72	6.17
	13-0828	1.90	0.59	5.37
	13-0851	3.70	0.66	4.47
	13-0852	4.60	0.68	1.07
	13-0853	5.80	0.72	2.78
	13-0854	3.70	0.70	2.40
159 mg/kg	Mean	3.520	0.680	3.432
	SD	1.119	0.075	1.794
	13-0801	2.80	0.70	
	13-0802	2.20	0.54	1.87
	13-0803	3.10	0.62	3.21
	13-0804	3.70	0.77	2.28
	13-0829	3.30	0.49	4.50
	13-0830	3.70	0.66	5.78
	13-0837	3.20	0.56	1.56
	13-0838	3.80	0.49	0.48
	13-0849	4.50	0.74	1.33
	13-0850	4.10	0.65	1.79
318 mg/kg	Mean	3.440	0.622	2.532
	SD	0.664	0.100	1.677
	13-0795	4.90	0.56	2.85
	13-0796	2.40	0.43	1.65
	13-0805	2.50	0.61	1.47
	13-0806	2.30	0.36	3.45
	13-0813	2.20	0.40	2.48
	13-0814	2.20	0.37	1.15
	13-0825	2.00	0.28	1.75
	13-0826	2.40	0.37	2.01
	13-0839	1.60	0.30	1.33
	13-0840	2.50	0.52	2.40
	Mean	2.500	0.420*	2.054
	SD	0.886	0.110	0.733

*Significantly different from control

Table M-2
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
14-Day Individual Thyroid Hormones
Male Rats

Group	Animal ID	Total T ₄ (ug/dL)	Total T ₃ (ng/mL)	TSH (ng/mL)
Control	13-0855	4.40	0.82	5.23
	13-0856	4.20	0.73	10.23
	13-0873	3.50	0.55	4.15
	13-0874	4.00	0.55	2.97
	13-0879	3.40	0.53	4.47
	13-0880	4.00	0.61	3.27
	13-0891	3.50	0.63	2.67
	13-0892	3.60	0.51	2.08
	13-0901	4.50	0.65	2.48
	13-0902	3.30	0.56	2.48
	Mean	3.840	0.614	4.002
	SD	0.435	0.098	2.409
47 mg/kg	13-0861	4.30	0.65	1.79
	13-0862	5.20	0.68	3.97
	13-0865	5.40	0.62	3.15
	13-0866	3.90	0.62	4.47
	13-0869	4.00	0.52	2.00
	13-0870	4.30	0.47	1.56
	13-0889	3.60	0.45	1.87
	13-0890	4.40	0.44	3.03
	13-0911	3.70	0.49	3.71
	13-0912	4.20	0.63	13.48
	Mean	4.300	0.557	3.901
	SD	0.591	0.092	3.513
93 mg/kg	13-0859	3.60	0.47	3.15
	13-0860	5.30	0.56	3.32
	13-0875	3.70	0.47	4.62
	13-0876	4.60	0.63	3.66
	13-0881	5.50	0.54	1.75
	13-0882	5.50	0.59	4.29
	13-0899	4.30	0.51	1.15
	13-0900	2.70	0.64	2.08
	13-0909	3.90	0.48	4.18
	13-0910	4.70	0.58	3.21

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185 mg/kg	Mean	4.380	0.547	3.141
	SD	0.921	0.064	1.150
	13-0867	4.00	0.55	5.46
	13-0868	4.20	0.49	3.27
	13-0877	5.00	0.50	1.79
	13-0878	2.80	0.24	
	13-0883	2.10	0.29	2.01
	13-0884	3.70	0.32	2.01
	13-0897	4.00	0.52	2.67
	13-0898	6.00	0.77	2.28
	13-0903	2.60	0.24	3.03
	13-0904	3.80	0.57	3.38
370 mg/kg	Mean	3.820	0.449*	2.877
	SD	1.148	0.172	1.128
	13-0857	1.80		1.14
	13-0858	1.60		1.75
	13-0871			
	13-0872	2.20	0.21	1.15
	13-0893	1.30		2.25
	13-0894			
	13-0895	1.80		4.13
	13-0896	1.10	0.23	2.47
	13-0905	2.90	0.24	3.03
	13-0906		0.22	1.47
741 mg/kg	Mean	1.814*	0.225*	2.174*
	SD	0.598	0.013	1.030
	13-0863	2.00		1.75
	13-0864			2.69
	13-0885	2.10		1.14
	13-0886			
	13-0887			
	13-0888	2.50	0.28	1.47
	13-0907			
	13-0908	2.80	0.30	1.14
	13-0913			
	13-0914	2.00	0.39	2.01
	Mean	2.280*	0.323*	1.700*
	SD	0.356	0.059	0.590

*Significantly different from control

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Appendix N

Histopathology Summary Table and Report

Toxicity Report No. S.0015656-13, July–August 2013

Table N-1
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats
14-Day Histopathology Summary Incidence and Severity
Female Rats

Tissue/Observation		Sodium Periodate Group (mg/kg-day)					
		control	20	40	80	159	318
Adrenal Glands	Number Examined:	10	10	10	10	10	10
Brain	Number Examined:	10	10	10	10	10	10
Heart	Number Examined:	10	10	10	10	10	10
Cardiomyopathy		0	0	0	0	0	1
	Average Severity:	0	0	0	0	0	1
Intestine, Large	Number Examined:	10	10	10	10	10	10
Inflammation		0	0	0	0	0	1
	Average Severity:	0	0	0	0	0	1
Mononuclear cell infiltrate, muscle wall		0	0	0	0	0	1
	Average Severity:	0	0	0	0	0	2
Intestine, Small	Number Examined:	10	10	10	10	10	10
Mineralization, peyer's patch		0	0	0	1	0	1
	Average Severity:	0	0	0	2	0	2
Kidneys	Number Examined:	10	10	10	10	10	10
Accumulation Hyaline Droplets		0	0	0	0	0	2
	Average Severity:	0	0	0	0	0	1.5
Dilated pelvis		0	0	0	0	1	0
	Average Severity:	0	0	0	0	1	0
Mineralization		1	4	3	1	2	0
	Average Severity:	1	1	1	1	1	0
Necrosis		0	0	0	0	0	3
	Average Severity:	0	0	0	0	0	1.7
Nephropathy		0	0	2	1	1	2
	Average Severity:	0	0	1	1	1	1
Liver	Number Examined:	10	10	10	10	10	10
Mononuclear cell infiltrate		9	6	7	6	6	4
	Average Severity:	1	1	1	1	1	1
Necrosis		0	0	0	0	0	1

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	Average Severity:	0	0	0	0	0	1
Vacuolization Cytoplasm		2	0	2	0	0	0
	Average Severity:	1	0	1	0	0	0
Lungs	Number Examined:	0	0	1	0	0	0
Lymph Nodes, Mesenteric	Number Examined:	0	0	0	0	0	1
Hemorrhage		0	0	0	0	0	1
	Average Severity:	0	0	0	0	0	2
Infiltrate, histiocyte		0	0	0	0	0	1
	Average Severity:	0	0	0	0	0	3
Ovaries	Number Examined:	10	10	10	10	10	10
Salivary Gland	Number Examined:	0	0	0	0	0	0
Spleen	Number Examined:	10	10	10	10	10	10
Deformity		1	0	0	0	0	0
	Average Severity:	2	0	0	0	0	0
Red pulp atrophy		0	0	0	0	0	4
	Average Severity:	0	0	0	0	0	2
White pulp atrophy		0	0	1	0	0	6
	Average Severity:	0	0	2	0	0	1.8
Stomach	Number Examined:	10	10	10	10	10	10
Erosion/ulcer, forestomach		0	0	0	0	0	1
	Average Severity:	0	0	0	0	0	1
Hemorrhage		0	0	0	0	0	2
	Average Severity:	0	0	0	0	0	2
Infiltrate, eosinophil		2	8	3	4	3	1
	Average Severity:	1	1	1	1	1	1
Inflammation		0	0	0	0	0	2
	Average Severity:	0	0	0	0	0	1
Necrosis, glandular stomach		0	0	0	0	0	2
	Average Severity:	0	0	0	0	0	1
Thymus	Number Examined:	10	10	9	10	10	10
Atrophy		2	2	1	2	3	9
	Average Severity:	1	1	1	1	1	2.2
Epithelial cell hyperplasia		0	0	0	0	1	0
	Average Severity:	0	0	0	0	1	0
Thyroid Glands	Number Examined:	10	10	10	10	10	10

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	Follicular cell hypertrophy/height	10	10	10	10	10	10
	Average Severity:	1.8	2	1.8	1.7	1.7	1.4
Tongue	Number Examined:	0	0	0	0	0	0
Uterus	Number Examined:	10	10	10	10	10	10
	Dilation	4	4	3	2	4	3
	Average Severity:	1	1	1	1	1	1
	Endometrial hyperplasia	0	1	1	2	1	0
	Average Severity:	0	1	1	1	1	0

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Table N-2
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

14-Day Histopathology Summary Incidence and Severity
Male Rats

Tissue/Observation		Sodium Periodate Group (mg/kg-day)					
		control	47	93	185	370	741
Adrenal Glands	Number Examined:	10	10	10	10	9	8
Hyperplasia		0	0	0	1	0	0
	Average Severity:	0	0	0	1	0	0
Vacuolization, zona fasciculata		0	1	0	1	0	0
	Average Severity:	0	2	0	2	0	0
Brain	Number Examined:	10	10	10	10	9	8
Hemorrhage		0	0	0	0	0	1
	Average Severity:	0	0	0	0	0	2
Epididymis	Number Examined:	10	10	10	10	9	8
Granuloma		0	0	0	1	0	1
	Average Severity:	0	0	0	4	0	2
Hypospermia		0	0	0	1	0	0
	Average Severity:	0	0	0	3	0	0
Heart	Number Examined:	10	10	10	10	9	8
Cardiomyopathy		1	0	0	1	0	0
	Average Severity:	1	0	0	1	0	0
Intestine, Large	Number Examined:	10	10	10	10	9	8
Hemorrhage		0	0	0	0	0	1
	Average Severity:	0	0	0	0	0	1
Inflammation		0	0	0	1	0	1
	Average Severity:	0	0	0	1	0	1
Mononuclear cell infiltrate, muscle wall		0	0	0	1	0	0
	Average Severity:	0	0	0	2	0	0
Intestine, Small	Number Examined:	10	10	10	10	9	8
Granuloma, peyer's patch		1	0	0	0	0	0
	Average Severity:	1	0	0	0	0	0
Inflammation		0	0	0	1	0	0
	Average Severity:	0	0	0	2	0	0
Kidneys	Number Examined:	10	10	10	10	9	8
Accumulation Hyaline Droplets		0	0	0	0	0	2

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	Average Severity:	0	0	0	0	0	2
Dilatation		0	0	1	0	0	0
	Average Severity:	0	0	1	0	0	0
Dilated pelvis		0	0	1	0	0	0
	Average Severity:	0	0	1	0	0	0
Inflammation		0	0	0	0	1	0
	Average Severity:	0	0	0	0	1	0
Lymphocytic infiltrate		1	0	0	0	0	0
	Average Severity:	1	0	0	0	0	0
Mineralization		0	0	0	1	3	3
	Average Severity:	0	0	0	1	1.7	1
Necrosis		0	0	0	1	7	6
	Average Severity:	0	0	0	3	2	1.5
Nephropathy		4	6	6	7	3	1
	Average Severity:	1	1	1	1	1	1
Liver	Number Examined:	10	10	10	10	9	8
Mononuclear cell infiltrate		10	9	9	7	2	2
	Average Severity:	1	1	1	1	1.5	1
Necrosis		0	1	0	0	1	1
	Average Severity:	0	1	0	0	4	2
Vacuolization Cytoplasm		10	6	8	0	2	0
	Average Severity:	1	1	1	0	1.5	0
Lungs	Number Examined:	0	0	0	0	0	0
Lymph Nodes, Mesenteric	Number Examined:	0	0	0	0	4	6
Atrophy		0	0	0	0	2	4
	Average Severity:	0	0	0	0	2	1.3
Hemorrhage		0	0	0	0	4	6
	Average Severity:	0	0	0	0	3.5	3.5
Salivary Gland	Number Examined:	0	0	0	0	1	0
Atrophy		0	0	0	0	1	0
	Average Severity:	0	0	0	0	4	0
Spleen	Number Examined:	10	10	10	10	9	8
Extramedullary hematopoiesis, increased		1	0	0	1	0	0
	Average Severity:	2	0	0	2	0	0
Red pulp atrophy		0	0	0	1	8	8
	Average Severity:	0	0	0	3	1.5	2
White pulp atrophy		0	1	0	3	8	8

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	Average Severity:	0	1	0	1.7	2	2.5
Stomach	Number Examined:	10	10	10	10	9	8
Erosion/ulcer, forestomach		0	0	0	1	2	2
	Average Severity:	0	0	0	2	2.5	3
Hemorrhage		0	0	0	0	3	2
	Average Severity:	0	0	0	0	1	1
Infiltrate, eosinophil		1	2	2	0	2	4
	Average Severity:	1	1	1	0	1	1.3
Inflammation		0	0	0	1	4	3
	Average Severity:	0	0	0	3	1.8	1.7
Necrosis, glandular stomach		0	0	0	1	4	5
	Average Severity:	0	0	0	1	1	1
Testes	Number Examined:	10	10	10	10	9	8
Degeneration		1	2	0	4	9	6
	Average Severity:	1	1	0	1.3	1.3	1
Thymus	Number Examined:	10	10	10	10	9	8
Atrophy		2	1	2	5	9	8
	Average Severity:	1	3	1	1	2.8	3.1
Thyroid Glands	Number Examined:	10	10	10	10	9	8
Follicular cell hypertrophy/height		10	10	10	10	9	8
	Average Severity:	2.4	2.2	2.4	2	1.9	1.8
Tongue	Number Examined:	0	0	0	0	0	1

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Appendix O

Summary of Benchmark Dose Model Results

Toxicity Report No. S.0015656-13, July–August 2013

Table O-1
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

Benchmark Dose Modeling Results
Female Rats

	Exponential2	Exponential3	Exponential4	Exponential5	Hill	Linear	Polynomial	Polynomial	Power
Estimated Values of Interest	Array	Array	Array	Array					
Table of Data and Estimated Values of Interest					Array	Array	Array	Array	Array
Specified Effect	1	1	1	1	1	1	1	1	1
Risk Type	SD	SD	SD	SD	SD	SD	SD	SD	SD
BMD	140.818	140.818	33.0523	33.0523	33.7317	115.97	0	-9999	115.97
BMDL	100.803	100.803	17.9399	17.9399	15.8527	78.275			78.275
p-value Test 1: Lack dose response?	< 0.0001	< 0.0001	< 0.0001	< 0.0001	<.0001	<.0001	<.0001	<.0001	<.0001
p-value Test 2: Constant variance?	0.4816	0.4816	0.4816	0.4816	0.4816	0.4816	0.4816	0.4816	0.4816
p-value Test 3: Good variance model?	0.3547	0.3547	0.3547	0.3547	0.3547	0.3547	0.3547	0.3547	0.3547

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p-value for fit: Does the model for the mean fit?	0.01064	0.01064	0.6687	0.6687	0.5258	0.02547	<.0001	<.0001	0.02547
AIC	381.947	381.947	372.3723	372.3723	374.09884	379.91291	8	411.221404	379.91291
Scaled residual for dose group near BMD	1.14	1.14	-0.2965	-0.2965	-0.343	2.27	-638000000	-3.21	2.27

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Table O-2
Protocol No.30-13-06-01
Acute and Subacute Oral Toxicity of Periodate in Rats

Benchmark Dose Modeling Results
Male Rats

	Exponential2	Exponential3	Exponential4	Exponential5	Hill	Linear	Polynomial	Polynomial	Power
Estimated Values of Interest	Array	Array	Array	Array					
Table of Data and Estimated Values of Interest					Array	Array	Array	Array	Array
Specified Effect	1	1	1	1	1	1	1	1	1
Risk Type	SD	SD	SD	SD	SD	SD	SD	SD	SD
BMD	182.219	182.219	56.3807	56.3807	52.796	122.591	0	0	122.591
BMDL	119.83	119.83	32.4267	32.4267	36.3848	78.9452			78.9452
p-value Test 1: Lack dose response?	< 0.0001	< 0.0001	< 0.0001	< 0.0001	<.0001	<.0001	<.0001	<.0001	<.0001
p-value Test 2: Constant variance?	0.001375	0.001375	0.001375	0.001375	0.001375	0.001375	0.001375	0.001375	0.001375
p-value Test 3: Good variance model?	0.03037	0.03037	0.03037	0.03037	0.03037	0.03037	0.03037	0.03037	0.03037

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p-value for fit: Does the model for the mean fit?	0.005926	0.005926	0.4185	0.4185	0.3725	0.04847	<.0001	<.0001	0.04847
AIC	391.1555	391.1555	381.512	381.512	381.8078	386.24435	8	10	386.24435
Scaled residual for dose group near BMD	1.042	1.042	0.8672	0.8672	0.779	0.68	- 1330000000	- 1030000000	0.68

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Appendix P

Study Protocol with Modifications

July 29, 2014

Commander
U.S. Army Public Health Command
ATTN: MCPO-EA (Ms. Tina Allen)
5158 Blackhawk Road
Aberdeen Proving Ground, Maryland 21010-5422
Tina.allen@us.army.mil
410-436-7208

RE: Contract No. CBRNIAC TAT CB-12-0356

Dear Ms. Allen:

Enclosed is a summary report titled *Histopathologic Changes in Young Rats as a Result of Exposure to Sodium Periodate and 5 Aminotetrazole* prepared under CBRNIAC Contract No. SP0-700-00-D-3180, Delivery Order Number 0750, Task CB-12-0356. If you have any questions please call Joseph Payne at (410) 306-8621.

Sincerely,



James Beddard, MS, MPH, FACHE
Director
Medical Readiness and Response

Enclosures

cc: CBRNIAC, w/ enclosure CBIAC_deliverable@battelle.org
Dhiraj. G. Parekh, COTR, w/ enclosure dhirajlal.g.parekh.civ@mail.mil
Jena Heddings, DTIC-I, w/o enclosure jennifer.j.heddings.civ@dtic.mil
Brian Stricker, PCO, w/o enclosure afica.kd.iac@us.af.mil
T. J. Reaster, Contract Administrator, w/o enclosure Thomas.Reaster@dcma.mil
Battelle Records Management, w/enclosure, recordsmgmt@battelle.org

Delivery Order Number 0750
CBRNIAC Task Number CB-12-0356

***Histopathologic Changes in Young Rats as a Result of Exposure to
Sodium Periodate and 5 Aminotetrazole
January 2014 – July 2014***

Prepared For:
***U.S. Army Public Health Command
5158 Blackhawk Road
Aberdeen Proving Ground, Maryland 21010-5422
Ms. Tina Allen
tina.allen@us.army.mil
(410) 436-7208***

July 29, 2014



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Submitted by:
Allen Singer, (614) 424-7444, singera@battelle.org
Additional author: Anthony J. Skowronek, (614) 424-7259, skowroneka@battelle.org

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14. ABSTRACT This study evaluated the histopathologic changes that occurred in young male and female rats as a result of exposure to sodium periodate by gavage over 14 days at targeted dosages up to 741 (males) or 318 (females) mg/kg/day, and exposure to 5-aminotetrazole (5-AT) up to 14 days at targeted dosages up to 621 mg/kg/day.					
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1. Anatomic Pathology Narrative Summary – Acute and Subchronic Oral Toxicity of Periodate in Rats.

1.1. PURPOSE

The purpose of this study was to determine the toxicity of the test substance, sodium periodate, when administered by gavage to male and female Sprague-Dawley rats for up to 14 days.

1.2. BACKGROUND

Periodate salts, compounds rich in oxygen and iodine, are being developed as replacements for perchlorate as oxidizers in pyrotechnic formulations. Alternatives to perchlorate usage are being pursued due to health and environmental concerns. This study evaluated the histopathologic changes that occurred in male and female rats as a result of exposure to perchlorate salt, sodium periodate, by gavage over 14 days at dosages up to 741 mg/kg/day (males) and 318 mg/kg/day (females).

1.3. METHODOLOGY

Protocol design dictated that necropsies were performed by trained prosectors at the testing facility. Organ weights were recorded manually on individual animal necropsy reports (USACHPPM Form 333-E, Sep 97)¹ for adrenals, brain, epididymides, heart, kidneys, liver, ovaries, spleen, testes, thymus, and uterus (where appropriate); these organs were also collected and preserved in appropriate fixative(s) per protocol design. The thyroid gland (with parathyroid glands) was collected and fixed at necropsy, and weighed for organ weight determinations post-fixation. In addition, other protocol-specified tissues, including peripheral nerve, skeletal muscle, spinal cord, eye with optic nerve, gastrointestinal tract, urinary bladder, lung, trachea, bone/marrow, pituitary gland, vagina, and any gross lesions were also collected and fixed. After tissues were fixed, protocol-specified tissues were packaged and shipped to Battelle, Columbus, Ohio for routine processing, sectioning, staining, and histopathologic examination by a board-certified veterinary pathologist.

1.4. SCOPE

As defined in the protocol for the subacute phase, 60 male rats were randomized into six groups of 10 rats each and 60 female rats were similarly divided into six additional groups of 10 rats each. For Battelle pathology processing and initial microscopic review, these 12 groups were then randomized and blinded, so that Battelle did not initially know which rat belonged to which group, or which group was given control or test substance. After initial microscopic review, the animals and groups were unblinded. Vehicle control male and female rats (blinded Groups 12 and 2, respectively) were dosed daily with distilled water; while blinded male Groups 11, 9, 7, 8 or 10 were administered targeted dosages of 46.31, 92.63, 182.25, 370.5, or 741 mg/kg/day (respectively) of sodium periodate by oral gavage. Female Groups 5, 3, 4, 1 or 6 were gavaged

¹ On October 1, 2009 the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) became the U.S. Army Public Health Command (USAPHC).

with targeted dosages of sodium periodate at 19.88, 39.75, 79.5, 159, or 318 mg/kg/day (respectively). Rats were exposed to vehicle control or test substance for 14 consecutive days (unless terminated moribund or unscheduled death occurred) and then submitted for necropsy.

1.5. SUMMARY

Oral exposure to sodium periodate in male and female rats for up to 14 days resulted in gross and/or microscopic evidence of periodate toxicity as observed in the thymus, spleen, kidneys, stomach, mesenteric lymph nodes, liver, and intestine. A no-observable effect level (NOEL) is suggested approximately at 92.63 mg/kg/day (males) to 159 mg/kg/day (females).

2. Anatomic Pathology Narrative Summary – Effects of Acute Oral 5-Aminotetrazole (5-AT) Exposure to Rats (*Rattus norvegicus*)

2.1. PURPOSE

The purpose of this study was to assess the toxicity of a new experimental explosive modifier, 5-aminotetrazole (5-AT), in Sprague-Dawley rats.

2.2. BACKGROUND

Perchlorate is an explosive substance that is currently fielded by the US Army. Perchlorate is known to interfere with iodide uptake in the thyroid gland and as such, the U.S. Environmental Protection Agency is moving towards setting containment levels and other regulations; thus there is a need for a suitable replacement for perchlorate. 5-AT is being considered as a replacement for perchlorate as an explosive modifier.

2.3. METHODOLOGY

Protocol design dictated that necropsies were performed by trained prosectors at the testing facility. Organ weights were recorded manually on individual animal necropsy reports (CHPPM Form 333-E, Sep 97) for adrenals, brain, epididymides, heart, kidneys, liver, ovaries, spleen, testes, thymus, and uterus (where appropriate); these organs were also collected and preserved in appropriate fixative(s) per protocol design. After tissues were fixed, selected protocol-specified tissues (liver, kidney, spleen, heart) were packaged and shipped to Battelle, Columbus, Ohio for routine processing, sectioning, staining, and histopathologic examination by a board-certified veterinary pathologist.

2.4. SCOPE

As defined in the protocol, 84 rats were divided into six exposure groups and one vehicle control group. Rats were orally administered 5-AT for up to 14 days at escalating doses (0, 22, 44, 88, 175, 310, or 621 mg/kg/day) and then necropsied. Liver, kidney, spleen and heart collected from 0 mg/kg/day rats (males and females) and 621 mg/kg/day rats (high dose males and females)

were submitted to Battelle for routine processing to slides (stained with hematoxylin and eosin) and histopathologic examination.

2.5. SUMMARY

There were no gross, microscopic and/or organ weight findings related to exposure of 5-AT for 14 days to male and female rats at a concentration of 621 mg/kg/day.

ANNEX A: Anatomic Pathology Narrative – Acute and Subacute Oral Toxicity Of Periodate In Rats

ANATOMIC PATHOLOGY NARRATIVE

ACUTE AND SUBACUTE ORAL TOXICITY OF PERIODATE IN RATS

Battelle Study No. 12918
USAPHC Study No. 30-13-06-01

July 29, 2014

Prepared By:

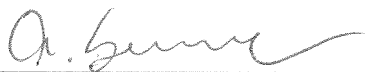


Allen W. Singer, D.V.M., D.A.B.T.
Diplomate, A.C.V.P.
Study Pathologist

7-29-14

Date

Approved By:



Anthony J. Skowronek, D.V.M., Ph.D.
Diplomate, A.C.V.P.
Technical Review

7/29/14

Date

BATTELLE
Columbus Operations
505 King Avenue
Columbus, Ohio 43201

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COMPLIANCE STATEMENT

This pathology investigation was conducted in a manner consistent with the principles of the United States Environmental Protection Agency (USEPA) Good Laboratory Practice regulations of the Toxic Substances Control Act (TSCA), as detailed in 40 CFR Part 792, plus amendments. Data were collected using the Next Generation PATH/TOX SYSTEM, V. 1.7.2 Build 37 (Xybion Medical Systems Corporation, Morris Plains, NJ), which has been validated for use on regulated studies by Battelle, Columbus, OH.



Allen W. Singer, D.V.M., D.A.B.T.
Diplomate, A.C.V.P.
Principal Investigator


7-29-14

Date

QUALITY ASSURANCE STATEMENT

This study was inspected by the Quality Assurance Unit and reports were submitted to the study director and management as follows:

Phase Inspected	Date Inspected	Date Reported to Battelle Principal Investigator and Management	Date of Report to Offsite Study Director and Management
Slide staining	12/16/2013	12/17/2013	12/17/2013
Audit study file	6/24/2014	6/25/2014	6/25/2014
Audit draft anatomic pathology narrative	6/24/2014	6/25/2014	6/25/2014
Audit final anatomic pathology narrative	7/29/2014	7/29/2014	7/29/2014



Quality Assurance Unit

7-29-14

Date

1.0 INTRODUCTION

The objective of this study was to determine the potential toxicity of the test substance, sodium periodate, when administered daily by gavage to male and female Sprague-Dawley rats for up to 14 days. The in-life study was conducted at the Army Institute of Public Health, U.S. Army Public Health Command, at Aberdeen Proving Ground (Edgewood Area), MD, 21010-5403, under approved protocol 30-13-06-01. The sponsoring agency was the U.S. Army Research Development and Engineering Command, Environmental Acquisition and Logistics Sustainment Program, Aberdeen Proving Ground, MD, 21005. As defined in the protocol for the subacute phase, 60 male rats were randomized into six groups of 10 rats each and 60 female rats were similarly divided into six additional groups of 10 rats each.

For Battelle pathology processing and initial microscopic review, these 12 groups were then randomized and blinded, so that Battelle did not initially know which rat belonged to which group, or which group was given control or test substance. After initial microscopic review, the animals and groups were unblinded. Vehicle control male and female rats (blinded Groups 12 and 2, respectively) were dosed daily with distilled water; while blinded male Groups 11, 9, 7, 8 or 10 were administered targeted dosages of 46.31, 92.63, 182.25, 370.5, or 741 mg/kg/day (respectively) of sodium periodate by oral gavage. Female Groups 5, 3, 4, 1 or 6 were gavaged with targeted dosages of sodium periodate at 19.88, 39.75, 79.5, 159, or 318 mg/kg/day (respectively). Rats were exposed to vehicle control or test substance for 14 consecutive days (unless terminated moribund or unscheduled death occurred) and then submitted for necropsy.

2.0 PATHOLOGY

2.1 Necropsy

Protocol design dictated that necropsies were performed by trained prosectors at the testing facility. Organ weights were recorded manually on individual animal necropsy reports (CHPPM Form 333-E, Sep 97) for adrenals, brain, epididymides, heart, kidneys, liver, ovaries, spleen, testes, thymus, and uterus (where appropriate); these organs were also collected and preserved in appropriate fixative(s) per protocol design. The thyroid gland (with parathyroids) was collected and fixed at necropsy, and weighed for organ weight determinations post-fixation. In addition, other protocol-specified tissues, including peripheral nerve, skeletal muscle, spinal cord, eye with optic nerve, gastrointestinal tract, urinary bladder, lung, trachea, bone/marrow, pituitary gland, vagina, and any gross lesions were also collected and fixed for potential histopathologic examination.

After tissues were fixed, specified tissues from the protocol were packaged and shipped to Battelle, Columbus, Ohio for processing and histopathologic examination. Necropsy Reports were included with this submission, but as noted above, did not

initially contain any dosage identifiers. Thus, specimens were processed and initially examined microscopically in “blinded” fashion (without knowledge of dosage assignment). Once the slides were examined, the raw blinded data were submitted to the Study Director for review, and the case numbers were “unblinded” (identified as to treatment or control group). Copies of the raw blinded data and confirmation of the Study Director instructions are contained in the Battelle Contributing Scientist Report *Study File*, but are not reported herein. This narrative reports only the data with identified group assignments, and all following interpretations and conclusions are made from that completed data set. For purposes of tabulation within this pathology report, groups are identified as belonging to one of the 12 groups noted previously, with dosages listed at the top of summary report tables.

Two Group 10 (741 mg/kg/day) males (13-0886 and 13-0913) and one Group 8 (370.5 mg/kg/day) male (13-0871) died on study after-hours and were not submitted for necropsy, thus no tissues were available for processing and examination for these animals. All other rats, including others found dead or killed early due to moribund condition, were necropsied per protocol. No Group 8 or 10 males survived to study conclusion.

All necropsied males had organ weight collections, even though early death animals obviously were younger by several days than those that survived to study conclusion. Although organ weight data, as recorded on the Necropsy Reports, were not statistically analyzed by the undersigned, a visual comparison of treated rat organ weight data with those from the same-sex controls was made. Generally, it appeared that the absolute thymus weights of males exposed to 182.25 mg/kg/day or greater were decreased in weight when compared to those of the control males. Similarly, but to a lesser degree, spleen and testes weights at the higher dosage(s) were also decreased in weight when compared to control male organ weights.

In females, five Group 6 (highest dosage, 318 mg/kg/day) rats were terminated early due to moribund condition. All other females survived to study termination, and all female rats were submitted to necropsy. Visual exam of the organ weight data, as recorded on each Necropsy Report, indicated that Group 6 female thymuses, and to a lesser extent, spleens, appeared to weigh less when these organ weights were compared to those of the controls.

There was substantial variation in thyroid weights across various groups of rats; these differences were interpreted to be within the biologic variation expected in young, growing rats. Organ weight data were not otherwise summarized or compiled for this contributing pathology report.

Changes interpreted to be related to test substance toxicity were noted grossly in multiple organs, including thymus (pale or small), spleen (pale, small, or dark), kidney (pale, brown, or red), stomach (blood/red, cyst, nodule, or raised area), and mesenteric lymph node (red). Liver “mottling or dark” were common macroscopic

observations in many rats, but did not have microscopic correlates except for a few rats, where treatment-associated hepatic necrosis was observed. Gross correlates were recorded as notes in the pathology data (Table 3, below).

Hydro-uterus was noted grossly in many females of all groups, and was seen microscopically to be due to physiologic morphologic changes expected in normal, cycling young rats. Thus, this, and other gross notations were considered to be incidental to periodate treatment.

2.2 Histopathology

Sections of adrenal glands, brain, epididymides, heart, intestine (large and small), kidneys, liver, ovaries, spleen, stomach, testes, thymus, thyroid, and uterus (as appropriate) were trimmed, slides prepared, and these were submitted for histologic examination. In addition, selected tissues with gross observations saved at necropsy were also trimmed, processed, and accompanied the slide set for examination. As noted previously, tissues were initially examined in “blind” fashion, without knowledge of treatment, dosage, or group assignment. Slides were examined by a board-certified veterinary pathologist, with diagnoses entered into the Next Generation PATH/TOX SYSTEM data-management system under “blind” mode. Diagnoses were rendered, transmitted to the Study Director, and then unblinded for producing summary incidence tables and this scientific narrative.

Except as noted in the microscopic tables, all organs listed as submitted were examined. Many female rats had only one ovary submitted for processing and review. When only one ovary was present, this was recorded as a note to the microscopic data table.

Summary incidences of unblinded microscopic observations are presented in Tables 1 (males) and 2 (females). For simplicity, unscheduled-death rats are included in these tables rather than separated into a second subset of incidence tables. Thus, each group contains 10 rats, except for male Groups 8 and 10 where one and two rats (respectively) died and were not submitted for necropsy.

Individual animal gross and microscopic pathology data are contained in Table 3; this table contains pathology data from each animal by group, beginning with Groups 7 to 12 (males) and then Groups 1 to 6 (females). Within each group, animals are listed sequentially. This ordering of animals and groups is a sequellae of the blinding/unblinding grouping process and was Xybion-driven. Gross observations are presented as “notes” in association with each animal, with various comments related to whether or not a given gross observation had a correlating lesion observed microscopically.

A variety of non-neoplastic lesions were noted in various tissues, and were semiquantitatively graded across a 4-point scale, where Grade 1 (minimal) referred to a minor change of negligible biologic significance or which affected less than

10 percent of the presented tissue area, and Grade 2 (mild) referred to a greater change which affected 10 to 19 percent of the tissue area. Grade 3 (moderate) was scaled to refer to a change of clear biologic relevance and which affected at least 20 percent of the tissue area; and Grade 4 (marked) was scaled for lesions considered to be of maximal morphologic change. For thyroid gland, an additional microscopic notation was made for all rats. Thyroid follicular epithelium was evaluated for increased size (hypertrophy and height) and graded on a 1 to 5 scale; when the follicular epithelium was predominately flattened, it was coded “1”; if it was essentially all tall columnar in morphology, that would constitute a Grade “5” (although there were no Grade 5’s). Mostly cuboidal-shaped epithelium constituted a Grade “3.” Grades 2 or 4 were used for variations between these appearances.

Treatment-related changes were observed in the thymus, spleen, kidneys, stomach, mesenteric lymph nodes, liver, and intestine sections in rats of one or both sexes, and the epididymides and testes of males.

Lesions were more frequent and more severe in higher-dose males, which also had higher group mortality, and received higher dosages than the comparable numerical group(s) of females.

Treatment-related changes in the thymus consisted of loss of cortical and/or medullary lymphocytes, or increased thymocyte apoptosis. While a few control or lower-dosage rats had minimal thymic atrophy, interpreted to be consistent with aging and involution, higher-dosage rats had mild to marked atrophy. A similar change was observed in the spleens of many rats given higher dosages of the test substance; morphologically this manifested itself as loss of lymphocytes in the splenic nodules, and was coded “atrophy, white pulp.” Also in the spleen, some higher-dosage rats had loss of extramedullary hematopoietic elements (red and white cell precursors) and contracted sinuses; this manifestation was coded “atrophy, red pulp.” These histologic changes correlated with gross notions of small thymus or spleen, as well as the apparent decreased thymic and spleen weights recorded at necropsy.

In the kidneys, higher-dosage rats frequently had acute tubular necrosis and/or eosinophilic hyaline droplets within renal tubular epithelium. Some such rats also had mineralization of necrotic cells, although a few control or lower dose rats also had scattered foci of mineral (which is occasionally seen in untreated rats). These changes corresponded to the gross notations of kidney discoloration (red/brown/pale).

In the stomach, treatment-related changes consisted of mucosal (epithelial cell) ulcer/erosion, or areas of necrosis, hemorrhage, or inflammation. These changes corresponded to gross notations of stomach – blood, cyst, nodule, or raised area.

Grossly, a few mesenteric lymph nodes in higher dosage rats were noted to be red; microscopically, these were confirmed as nodes with sinus hemorrhage with rare lymphocyte atrophy or sinus infiltration of histiocytes. These were also attributed to treatment with periodate.

A common gross notation of the liver was “liver – mottled.” Although most of these had no microscopic correlate and were presumably due to hepatic sinusoid congestion, a few higher-dosage rats had significant areas of hepatocellular necrosis, which was attributed to toxicity of periodate administration.

A few small and large intestinal sections in higher dosage rats had areas of inflammation, hemorrhage, or mononuclear cell infiltrate. These were attributed to toxic effects on the intestinal tract.

Finally, many higher dosage males had minimal to mild alterations of their testes. Morphologically, this consisted of seminiferous tubules containing fewer germinal epithelial cells, often leaving a larger and empty tubular lumen with fewer mature spermatozoa. Rarely, the epididymides also contained fewer spermatozoa than expected. These slight changes appeared to correspond with an apparent slight decrease in testes weights as recorded at necropsy. A similar morphologic appearance was noted in one control male (minimal) and several low-dosage males, so it was interpreted that *increased incidence* and *increased severity*, when compared to the controls, were the hallmarks of this treatment-related change.

Thyroid gland follicular epithelial grading did not reveal any noticeable change in animals treated with periodate when compared to results in the controls. A few other incidental changes were noted in the various organs examined, but none of these were interpreted to be of biologic or toxicologic relevance.

3.0 CONCLUSIONS

Oral exposure to sodium periodate in male and female rats for up to 14 days at concentrations of 182.25 mg/kg/day or above resulted in mortality. Although the concentrations administered to females were less than those administered to males, the mortality occurred at marginally similar levels, with half of females given 318 mg/kg/day and all of males given 370.5 or 741 mg/kg/day or higher not surviving to study termination.

Gross and/or microscopic evidence of periodate toxicity were observed in the thymus, spleen, kidneys, stomach, mesenteric lymph nodes, liver, and intestine sections in rats of one or both sexes, and the epididymides and testes of males. In the thymus, spleen, mesenteric lymph node, stomach and testes/epididymides, the toxic change was manifested as loss/necrosis of rapidly dividing epithelial cells. The observed acute tubular necrosis (with or without mineralization) and hyaline droplets in the kidney epithelial cells were attributed to local toxicity related to urinary excretion of high levels of periodate and/or a metabolite. Other changes noted in

organs examined (hepatic necrosis, hemorrhage or inflammation in several sites), that were attributed to toxicity, may be related to poor tissue perfusion or earlier (in the study timeline) epithelial cell death. The observed toxic effects on the blood cell components (red and white cells) were interpreted to be likely a direct effect of periodate exposure, and not related to endogenous stress, because scant evidence of increased adrenal cortical steroid production (increased cortical vacuolization) was present across the study rats. Bone marrow was not submitted for processing or examination, so the full spectrum of toxicity on marrow elements could not be evaluated. In a study of this short duration, it is unclear if mature circulating red or white cell populations would show any definitive effect.

Based on the tissues submitted for examination, a no-observable effect level (NOEL) is suggested approximately at 92.63 mg/kg/day (males) to 159 mg/kg/day (females). However, a few apparent treatment-related morphologies were noted in a few lower-dosage rats. Thus, a final NOEL should be based on the full spectrum of toxicologic data, including body weight gain, clinical pathology results, and statistical analysis of organ weight data.

4.0 STORAGE OF STUDY MATERIALS AND RECORDS RETENTION

Copies of the Battelle study records and final report will be archived and maintained at or under the direction of Battelle, according to testing facility SOP and EPA requirements. The Pathology specimens archived at Battelle (slides submitted from the USAPHC for examination herein) and study file will be returned to the USAPHC for archival.

Table 1. Incidence Summary of Microscopic Observations with Average Severity – Males, All Animals (Except 3)

Group Legend: 12-0 mg/kg/day; 7-182.25 mg/kg/day; 8-370.5 mg/kg/day; 9-92.63 mg/kg/day; 10-741 mg/kg/day; 11-46.31 mg/kg/day							
		Number Observed Per Group					
Tissue/Observation	Group:	12	7	8	9	10	11
Adrenal Glands	Number Examined:	10	10	9	10	8	10
Hyperplasia		0	1	0	0	0	0
	Average Severity:	0.0	1.0	0.0	0.0	0.0	0.0
Vacuolization, zona fasciculata		0	1	0	0	0	1
	Average Severity:	0.0	2.0	0.0	0.0	0.0	2.0
Brain	Number Examined:	10	10	9	10	8	10
Hemorrhage		0	0	0	0	1	0
	Average Severity:	0.0	0.0	0.0	0.0	2.0	0.0
Epididymis	Number Examined:	10	10	9	10	8	10
Granuloma		0	1	0	0	1	0
	Average Severity:	0.0	4.0	0.0	0.0	2.0	0.0
Hypospermia		0	1	0	0	0	0
	Average Severity:	0.0	3.0	0.0	0.0	0.0	0.0
Heart	Number Examined:	10	10	9	10	8	10
Cardiomyopathy		1	1	0	0	0	0
	Average Severity:	1.0	1.0	0.0	0.0	0.0	0.0
Intestine, Large	Number Examined:	10	10	9	10	8	10
Hemorrhage		0	0	0	0	1	0
	Average Severity:	0.0	0.0	0.0	0.0	1.0	0.0
Inflammation		0	1	0	0	1	0
	Average Severity:	0.0	1.0	0.0	0.0	1.0	0.0
Mononuclear cell infiltrate, muscle wall		0	1	0	0	0	0
	Average Severity:	0.0	2.0	0.0	0.0	0.0	0.0

Table 1. Incidence Summary of Microscopic Observations with Average Severity – Males, All Animals (Except 3) (Continued)

Group Legend: 12-0 mg/kg/day; 7-182.25 mg/kg/day; 8-370.5 mg/kg/day; 9-92.63 mg/kg/day; 10-741 mg/kg/day; 11-46.31 mg/kg/day							
		Number Observed Per Group					
Tissue/Observation	Group:	12	7	8	9	10	11
Intestine, Small	Number Examined:	10	10	9	10	8	10
Granuloma, peyer's patch		1	0	0	0	0	0
	Average Severity:	1.0	0.0	0.0	0.0	0.0	0.0
Inflammation		0	1	0	0	0	0
	Average Severity:	0.0	2.0	0.0	0.0	0.0	0.0
Kidneys	Number Examined:	10	10	9	10	8	10
Accumulation Hyaline Droplets		0	0	0	0	2	0
	Average Severity:	0.0	0.0	0.0	0.0	2.0	0.0
Dilatation		0	0	0	1	0	0
	Average Severity:	0.0	0.0	0.0	1.0	0.0	0.0
Dilated pelvis		0	0	0	1	0	0
	Average Severity:	0.0	0.0	0.0	1.0	0.0	0.0
Inflammation		0	0	1	0	0	0
	Average Severity:	0.0	0.0	1.0	0.0	0.0	0.0
Lymphocytic infiltrate		1	0	0	0	0	0
	Average Severity:	1.0	0.0	0.0	0.0	0.0	0.0
Mineralization		0	1	3	0	3	0
	Average Severity:	0.0	1.0	1.7	0.0	1.0	0.0
Necrosis		0	1	7	0	6	0
	Average Severity:	0.0	3.0	2.0	0.0	1.5	0.0
Nephropathy		4	7	3	6	1	6
	Average Severity:	1.0	1.0	1.0	1.0	1.0	1.0

Table 1. Incidence Summary of Microscopic Observations with Average Severity – Males, All Animals (Except 3) (Continued)

Group Legend: 12-0 mg/kg/day; 7-182.25 mg/kg/day; 8-370.5 mg/kg/day; 9-92.63 mg/kg/day; 10-741 mg/kg/day; 11-46.31 mg/kg/day							
		Number Observed Per Group					
Tissue/Observation	Group:	12	7	8	9	10	11
Liver	Number Examined:	10	10	9	10	8	10
Mononuclear cell infiltrate		10	7	2	9	2	9
	Average Severity:	1.0	1.0	1.5	1.0	1.0	1.0
Necrosis		0	0	1	0	1	1
	Average Severity:	0.0	0.0	4.0	0.0	2.0	1.0
Vacuolization Cytoplasm		10	0	2	8	0	6
	Average Severity:	1.0	0.0	1.5	1.0	0.0	1.0
Lungs	Number Examined:	0	0	0	0	0	0
Lymph Nodes, Mesenteric	Number Examined:	0	0	4	0	6	0
Atrophy		0	0	2	0	4	0
	Average Severity:	0.0	0.0	2.0	0.0	1.3	0.0
Hemorrhage		0	0	4	0	6	0
	Average Severity:	0.0	0.0	3.5	0.0	3.5	0.0
Salivary Gland	Number Examined:	0	0	1	0	0	0
Atrophy		0	0	1	0	0	0
	Average Severity:	0.0	0.0	4.0	0.0	0.0	0.0
Spleen	Number Examined:	10	10	9	10	8	10
Extramedullary hematopoiesis, increased		1	1	0	0	0	0
	Average Severity:	2.0	2.0	0.0	0.0	0.0	0.0
Red pulp atrophy		0	1	8	0	8	0
	Average Severity:	0.0	3.0	1.5	0.0	2.0	0.0
White pulp atrophy		0	3	8	0	8	1
	Average Severity:	0.0	1.7	2.0	0.0	2.5	1.0

Table 1. Incidence Summary of Microscopic Observations with Average Severity – Males, All Animals (Except 3) (Continued)

Group Legend: 12-0 mg/kg/day; 7-182.25 mg/kg/day; 8-370.5 mg/kg/day; 9-92.63 mg/kg/day; 10-741 mg/kg/day; 11-46.31 mg/kg/day							
		Number Observed Per Group					
Tissue/Observation	Group:	12	7	8	9	10	11
Stomach	Number Examined:	10	10	9	10	8	10
Erosion/ulcer, forestomach		0	1	2	0	2	0
	Average Severity:	0.0	2.0	2.5	0.0	3.0	0.0
Hemorrhage		0	0	3	0	2	0
	Average Severity:	0.0	0.0	1.0	0.0	1.0	0.0
Infiltrate, eosinophil		1	0	2	2	4	2
	Average Severity:	1.0	0.0	1.0	1.0	1.3	1.0
Inflammation		0	1	4	0	3	0
	Average Severity:	0.0	3.0	1.8	0.0	1.7	0.0
Necrosis, glandular stomach		0	1	4	0	5	0
	Average Severity:	0.0	1.0	1.0	0.0	1.0	0.0
Testes	Number Examined:	10	10	9	10	8	10
Degeneration		1	4	9	0	6	2
	Average Severity:	1.0	1.3	1.3	0.0	1.0	1.0
Thymus	Number Examined:	10	10	9	10	8	10
Atrophy		2	5	9	2	8	1
	Average Severity:	1.0	1.0	2.8	1.0	3.1	3.0
Thyroid Glands	Number Examined:	10	10	9	10	8	10
Follicular cell hypertrophy/height		10	10	9	10	8	10
	Average Severity:	2.4	2.0	1.9	2.4	1.8	2.2
Tongue	Number Examined:	0	0	0	0	1	0

Table 2. Incidence Summary of Microscopic Observations with Average Severity – Females, All Animals

Group Legend: 2-0 mg/kg/day; 1-159 mg/kg/day; 3-39.75 mg/kg/day; 4-79.5 mg/kg/day; 5-19.88 mg/kg/day; 6-318 mg/kg/day		Number Observed Per Group					
Tissue/Observation	Group:	2	1	3	4	5	6
Adrenal Glands	Number Examined:	10	10	10	10	10	10
Brain	Number Examined:	10	10	10	10	10	10
Heart	Number Examined:	10	10	10	10	10	10
Cardiomyopathy		0	0	0	0	0	1
	Average Severity:	0.0	0.0	0.0	0.0	0.0	1.0
Intestine, Large	Number Examined:	10	10	10	10	10	10
Inflammation		0	0	0	0	0	1
	Average Severity:	0.0	0.0	0.0	0.0	0.0	1.0
Mononuclear cell infiltrate, muscle wall		0	0	0	0	0	1
	Average Severity:	0.0	0.0	0.0	0.0	0.0	2.0
Intestine, Small	Number Examined:	10	10	10	10	10	10
Mineralization, peyer's patch		0	0	0	1	0	1
	Average Severity:	0.0	0.0	0.0	2.0	0.0	2.0
Kidneys	Number Examined:	10	10	10	10	10	10
Accumulation Hyaline Droplets		0	0	0	0	0	2
	Average Severity:	0.0	0.0	0.0	0.0	0.0	1.5
Dilated pelvis		0	1	0	0	0	0
	Average Severity:	0.0	1.0	0.0	0.0	0.0	0.0
Mineralization		1	2	3	1	4	0
	Average Severity:	1.0	1.0	1.0	1.0	1.0	0.0
Necrosis		0	0	0	0	0	3
	Average Severity:	0.0	0.0	0.0	0.0	0.0	1.7
Nephropathy		0	1	2	1	0	2
	Average Severity:	0.0	1.0	1.0	1.0	0.0	1.0

Table 2. Incidence Summary of Microscopic Observations with Average Severity – Females, All Animals (Continued)

Group Legend: 2-0 mg/kg/day; 1-159 mg/kg/day; 3-39.75 mg/kg/day; 4-79.5 mg/kg/day; 5-19.88 mg/kg/day; 6-318 mg/kg/day		Number Observed Per Group					
Tissue/Observation	Group:	2	1	3	4	5	6
Liver	Number Examined:	10	10	10	10	10	10
Mononuclear cell infiltrate		9	6	7	6	6	4
	Average Severity:	1.0	1.0	1.0	1.0	1.0	1.0
Necrosis		0	0	0	0	0	1
	Average Severity:	0.0	0.0	0.0	0.0	0.0	1.0
Vacuolization Cytoplasm		2	0	2	0	0	0
	Average Severity:	1.0	0.0	1.0	0.0	0.0	0.0
Lungs	Number Examined:	0	0	1	0	0	0
Lymph Nodes, Mesenteric	Number Examined:	0	0	0	0	0	1
Hemorrhage		0	0	0	0	0	1
	Average Severity:	0.0	0.0	0.0	0.0	0.0	2.0
Infiltrate, histiocyte		0	0	0	0	0	1
	Average Severity:	0.0	0.0	0.0	0.0	0.0	3.0
Ovaries	Number Examined:	10	10	10	10	10	10
Salivary Gland	Number Examined:	0	0	0	0	0	0
Spleen	Number Examined:	10	10	10	10	10	10
Deformity		1	0	0	0	0	0
	Average Severity:	2.0	0.0	0.0	0.0	0.0	0.0
Red pulp atrophy		0	0	0	0	0	4
	Average Severity:	0.0	0.0	0.0	0.0	0.0	2.0
White pulp atrophy		0	0	1	0	0	6
	Average Severity:	0.0	0.0	2.0	0.0	0.0	1.8

Table 2. Incidence Summary of Microscopic Observations with Average Severity – Females, All Animals (Continued)

Group Legend: 2-0 mg/kg/day; 1-159 mg/kg/day; 3-39.75 mg/kg/day; 4-79.5 mg/kg/day; 5-19.88 mg/kg/day; 6-318 mg/kg/day		Number Observed Per Group					
Tissue/Observation	Group:	2	1	3	4	5	6
Stomach	Number Examined:	10	10	10	10	10	10
Erosion/ulcer, forestomach		0	0	0	0	0	1
	Average Severity:	0.0	0.0	0.0	0.0	0.0	1.0
Hemorrhage		0	0	0	0	0	2
	Average Severity:	0.0	0.0	0.0	0.0	0.0	2.0
Infiltrate, eosinophil		2	3	3	4	8	1
	Average Severity:	1.0	1.0	1.0	1.0	1.0	1.0
Inflammation		0	0	0	0	0	2
	Average Severity:	0.0	0.0	0.0	0.0	0.0	1.0
Necrosis, glandular stomach		0	0	0	0	0	2
	Average Severity:	0.0	0.0	0.0	0.0	0.0	1.0
Thymus	Number Examined:	10	10	9	10	10	10
Atrophy		2	3	1	2	2	9
	Average Severity:	1.0	1.0	1.0	1.0	1.0	2.2
Epithelial cell hyperplasia		0	1	0	0	0	0
	Average Severity:	0.0	1.0	0.0	0.0	0.0	0.0
Thyroid Glands	Number Examined:	10	10	10	10	10	10
Follicular cell hypertrophy/height		10	10	10	10	10	10
	Average Severity:	1.8	1.7	1.8	1.7	2.0	1.4
Tongue	Number Examined:	0	0	0	0	0	0
Uterus	Number Examined:	10	10	10	10	10	10
Dilation		4	4	3	2	4	3
	Average Severity:	1.0	1.0	1.0	1.0	1.0	1.0
Endometrial hyperplasia		0	1	1	2	1	0
	Average Severity:	0.0	1.0	1.0	1.0	1.0	0.0

Table 3. Individual Gross and Microscopic Observations – Males and Females

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal			
#	Sex	Group	
13-0867	M	7	
			Intestine, Large (Required)
			Mononuclear cell infiltrate, muscle wall - Mild
			Kidneys (Required)
			Nephropathy - Minimal
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Testes (Required)
			Degeneration - Minimal, Germinal Epithelium
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Small
			Stomach
			Thymus
			Epididymis
			Spleen
13-0868	M	7	
			Adrenal Glands (Required)
			Hyperplasia - Minimal, zona fasciculata
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Spleen (Required)
			Extramedullary hematopoiesis, increased - Mild
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 3
			The following Tissues are Examined/Unremarkable:
			Brain
			Epididymis
			Heart
			Intestine, Large
			Intestine, Small
			Kidneys
			Stomach
			Testes
			Thymus
13-0877	M	7	
			Epididymis (Required)
			Hypospermia - Moderate

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal					
#	Sex	Group			
13-0877	M	7			
			Kidneys (Required)		
			Nephropathy - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Testes (Required)		
			Degeneration - Minimal, Germinal Epithelium		
			Thymus (Required)		
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Both thyroid lobes found and processed at trim for micro exam.		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Spleen
			Stomach		
13-0878	M	7			
			Intestine, Small (Required)		
			Inflammation - Mild		
			Kidneys (Required)		
			Gross observation (pale kidneys) correlate to diffuse renal tubule necrosis.		
			Mineralization - Minimal		
			Necrosis - Moderate, Renal Tubule, Subacute		
			Spleen (Required)		
			Gross observation (spleen small) due to red and white pulp atrophy noted microscopically.		
			Red pulp atrophy - Moderate		
			White pulp atrophy - Moderate		
			Stomach (Required)		
			Gross observation (inner lining of stomach sloughed) correlates with ulceration noted microscopically.		
			Erosion/ulcer, forestomach - Mild		
			Inflammation - Moderate, Acute		
			Necrosis, glandular stomach - Minimal		
			Testes (Required)		
			Degeneration - Mild, Germinal Epithelium		
			Thymus (Required)		
			Gross observation (thymus small) correlates with (lymphoid) atrophy noted microscopically.		

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal					
#	Sex	Group			
13-0878	M	7			
			Thymus (Required)	Gross observation (thymus small) correlates with (lymphoid) atrophy noted microscopically.	
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 1		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Liver
13-0883	M	7			
			Intestine, Large (Required)		
			Inflammation - Minimal, Focal		
			Kidneys (Required)		
			Nephropathy - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Spleen (Required)		
			White pulp atrophy - Minimal		
			Testes (Required)		
			Degeneration - Minimal, Germinal Epithelium		
			Thymus (Required)		
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Small	Stomach
13-0884	M	7			
			Kidneys (Required)		
			Nephropathy - Minimal		
			Liver (Required)	Gross observation (liver mildly mottled) has no microscopic correlation.	
			Mononuclear cell infiltrate - Minimal		

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0884	M	7	Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Intestine, Small
			Spleen	Stomach	Testes
			Thymus		
13-0897	M	7	Heart (Required)		
			Cardiomyopathy - Minimal		
			Thymus (Required)		
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Intestine, Large	Intestine, Small	Kidneys
			Liver	Spleen	Stomach
			Testes		
13-0898	M	7	Kidneys (Required)		
			Nephropathy - Minimal		
			Liver (Required)	Gross observation (dark liver) has no microscopic correlate.	
			Mononuclear cell infiltrate - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Intestine, Small
			Spleen	Stomach	Testes

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0898	M	7	The following Tissues are Examined/Unremarkable:		
			Thymus		
13-0903	M	7	Only one adrenal on slide, consistent with necropsy record.		
			Adrenal Glands (Required)		
			Vacuolization, zona fasciculata - Mild		
			Epididymis (Required)		
			Granuloma - Marked, Focal		
			Kidneys (Required)		
			Nephropathy - Minimal		
			Thymus (Required)		
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Brain	Heart	Intestine, Large
			Intestine, Small	Liver	Spleen
			Stomach	Testes	
13-0904	M	7			
			Kidneys (Required)		
			Nephropathy - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Spleen (Required)		
			White pulp atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Intestine, Small
			Stomach	Testes	Thymus

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0904	M	7	
13-0857	M	8	
			Brain (Required)
			Gross observation (blood, underside of brain) was noted to be due to agonal hemorrhage or congestion into meninges, and not diagnosed as a pathologic change.
			Kidneys (Required)
			Inflammation - Minimal, Mixed Cell
			Necrosis - Moderate, Renal Tubule, Acute
			Liver (Required)
			Gross observation (mild mottling on liver; 1 cm of white patches, extend into liver when cut) does not appear to have a microscopic correlate.
			Spleen (Required)
			Gross observation (spleen pale) corresponds microscopically with red pulp atrophy.
			Red pulp atrophy - Mild
			White pulp atrophy - Mild
			Stomach (Required)
			Gross observation (yellow fluid in stomach and areas of redness) correspond to erosions with inflammation, noted microscopically.
			Erosion/ulcer, forestomach - Mild
			Inflammation - Mild, Acute
			Testes (Required)
			Degeneration - Minimal, Germinal Epithelium
			Thymus (Required)
			Atrophy - Mild
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 1
			Lungs (Non required)
			Missing/Gross observation (lungs pale and spongy) noted, however lungs not saved or processed for histologic examination.
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Epididymis
			Heart
			Intestine, Large
			Intestine, Small
			Liver
13-0858	M	8	
			Kidneys (Required)
			Nephropathy - Minimal

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal					
#	Sex	Group			
13-0858	M	8			
			Spleen (Required)		
			Red pulp atrophy - Minimal		
			White pulp atrophy - Moderate		
			Stomach (Required)	Gross observation (2 mm fluid-filled cyst in glandular stomach) not present on slide for review; however edematous areas in non-glandular stomach, which may grossly appear to be cystic, correlated with areas of necrosis and inflammation (and edema, not diagnosed separately) on micro exam.	
			Erosion/ulcer, forestomach - Moderate		
			Inflammation - Moderate, Acute		
			Testes (Required)		
			Degeneration - Minimal, Germinal Epithelium		
			Thymus (Required)		
			Atrophy - Mild		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			Lymph Nodes, Mesenteric (Non required)	Gross observation (red mesenteric lymph nodes) corresponds to acute sinus hemorrhage on micro exam.	
			Atrophy - Mild, Lymphoid		
			Hemorrhage - Marked, sinus		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Intestine, Small
			Liver		
13-0872	M	8			
			Kidneys (Required)		
			Necrosis - Minimal, Renal Tubule, Acute		
			Spleen (Required)		
			Red pulp atrophy - Minimal		
			Stomach (Required)	Gross observation (glandular stomach mucosa very red) correlates with hemorrhage noted microscopically.	
			Hemorrhage - Minimal		
			Inflammation - Minimal, Acute		

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal			
#	Sex	Group	
13-0872	M	8	
			Gross observation (glandular stomach mucosa very red) correlates with hemorrhage noted microscopically.
			Stomach (Required)
			Necrosis, glandular stomach - Minimal
			Testes (Required)
			Degeneration - Minimal
			Thymus (Required)
			Atrophy - Moderate
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 3
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Liver
			Epididymis
			Intestine, Small
13-0893	M	8	
			Kidneys (Required)
			Mineralization - Minimal
			Necrosis - Moderate, Renal Tubule, Acute
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Spleen (Required)
			Red pulp atrophy - Minimal
			White pulp atrophy - Mild
			Stomach (Required)
			Hemorrhage - Minimal
			Inflammation - Minimal, Subacute
			Necrosis, glandular stomach - Minimal
			Testes (Required)
			Degeneration - Mild, Germinal Epithelium
			Thymus (Required)
			Atrophy - Moderate

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal					
#	Sex	Group			
13-0893	M	8			
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Intestine, Small
13-0894	M	8			
			Kidneys (Required)		
			Necrosis - Minimal, Renal Tubule, Acute		
			Nephropathy - Minimal		
			Liver (Required)		
			Gross notation (liver - mottled, dark) had no microscopic correlate.		
			Spleen (Required)		
			Red pulp atrophy - Moderate		
			White pulp atrophy - Moderate		
			Stomach (Required)		
			Gross notation (areas of redness throughout glandular stomach) corresponds microscopically to minimal epithelial necrosis with associated vascular congestion (congestion not diagnosed separately).		
			Necrosis, glandular stomach - Minimal, Acute		
			Testes (Required)		
			Degeneration - Mild, Germinal Epithelium		
			Thymus (Required)		
			Atrophy - Mild		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Intestine, Small
			Liver		
13-0895	M	8			
			Kidneys (Required)		
			Gross notation (medulla of both kidneys dark red) is likely due to congestion compatible with moribund state and death. Very minimal acute tubular necrosis in kidney is cortical and would not contribute to medullary discoloration.		

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal			
#	Sex	Group	
13-0895	M	8	
		Kidneys (Required)	Gross notation (medulla of both kidneys dark red) is likely due to congestion compatible with moribund state and death. Very minimal acute tubular necrosis in kidney is cortical and would not contribute to medullary discoloration.
		Necrosis - Minimal, Renal Tubule, Acute	
		Nephropathy - Minimal	
		Liver (Required)	Gross notation (liver dark with mottling) probably due to sinuoidal congestion (not diagnosed as a lesion of pathology), although increased mononuclear cell infiltrate within sinuoids may have contributed to appearance.
		Mononuclear cell infiltrate - Mild	
		Vacuolization Cytoplasm - Minimal	
		Spleen (Required)	
		White pulp atrophy - Mild	
		Stomach (Required)	
		Necrosis, glandular stomach - Minimal, Acute	
		Testes (Required)	
		Degeneration - Mild, Germinal Epithelium	
		Thymus (Required)	
		Atrophy - Marked	
		Thyroid Glands (Required)	
		Follicular cell hypertrophy/height - 2	
		The following Tissues are Examined/Unremarkable:	
		Adrenal Glands	Brain
		Heart	Intestine, Large
			Epididymis
			Intestine, Small
13-0896	M	8	
		Kidneys (Required)	Gross observation (light brown mottled cortex, bilateral with red medulla) corresponds to mineralization of tubules on micro exam; tubular changes are cortical, medulla discoloration presumed due to congestion (not diagnosed as a lesion of pathology).
		Mineralization - Moderate, Renal Tubule	
		Necrosis - Mild, Renal Tubule, Acute	
		Liver (Required)	

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0896	M	8	
			Liver (Required)
			Vacuolization Cytoplasm - Mild
			Spleen (Required)
			Red pulp atrophy - Mild
			White pulp atrophy - Mild
			Testes (Required)
			Degeneration - Minimal, Germinal Epithelium
			Thymus (Required)
			Atrophy - Moderate
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			Lymph Nodes, Mesenteric (Non required) Gross notation (red mesentery lymph nodes) corresponds to hemorrhage noted microscopically.
			Atrophy - Mild
			Hemorrhage - Moderate, sinus
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Stomach
			Epididymis
			Intestine, Small
13-0905	M	8	
			Spleen (Required)
			Red pulp atrophy - Minimal
			White pulp atrophy - Minimal
			Stomach (Required)
			Infiltrate, eosinophil - Minimal
			Testes (Required)
			Degeneration - Minimal, Germinal Epithelium
			Thymus (Required)
			Atrophy - Moderate
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 1

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0905	M	8	
			Lymph Nodes, Mesenteric (Non required) Gross observation (mesenteric lymph nodes red) correlates to sinus hemorrhage microscopically.
			Hemorrhage - Moderate, sinus
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands Brain Epididymis
			Heart Intestine, Large Intestine, Small
			Kidneys Liver
13-0906	M	8	
			Kidneys (Required) Gross observations (light brown mottled cortex, bilateral kidneys) corresponds to acute tubular necrosis with mineralization noted at micro exam.
			Mineralization - Minimal
			Necrosis - Moderate, Renal Tubule, Acute
			Liver (Required) Gross observation (several lobes have brown mottled areas) corresponds to massive centrilobular hepatocellular necrosis on micro exam.
			Necrosis - Marked, Centrilobular
			Spleen (Required)
			Red pulp atrophy - Minimal
			White pulp atrophy - Minimal
			Stomach (Required) Gross observation (patches of red in the glandular stomach) corresponds microscopically to minimal acute hemorrhage; occasional mineralized epithelial cells also noted but not diagnosed separately.
			Hemorrhage - Minimal
			Infiltrate, eosinophil - Minimal
			Testes (Required)
			Degeneration - Minimal, Germinal Epithelium
			Thymus (Required) Gross observation (pale thymus) corresponds to atrophy (necrosis) of cortical lymphocytes noted microscopically.
			Atrophy - Moderate
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			Lymph Nodes, Mesenteric (Non required) Gross observation (mesenteric lymph nodes are red) corresponds microscopically to sinus hemorrhage.
			Hemorrhage - Marked, sinus

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal					
#	Sex	Group			
13-0906	M	8			
13-0906	M	8			
		Salivary Gland (Non required)	Gross observation (salivary glands are white) corresponds microscopically to marked atrophy (with necrosis).		
		Atrophy - Marked			
		The following Tissues are Examined/Unremarkable:			
		Adrenal Glands	Brain	Epididymis	
		Heart	Intestine, Large	Intestine, Small	
13-0859	M	9			
		Liver (Required)			
		Mononuclear cell infiltrate - Minimal			
		Thymus (Required)			
		Atrophy - Minimal			
		Thyroid Glands (Required)			
		Follicular cell hypertrophy/height - 3			
		The following Tissues are Examined/Unremarkable:			
		Adrenal Glands	Brain	Epididymis	
		Heart	Intestine, Large	Intestine, Small	
		Kidneys	Spleen	Stomach	
		Testes			
13-0860	M	9			
		Kidneys (Required)			
		Dilated pelvis - Minimal, Unilateral			
		Nephropathy - Minimal			
		Liver (Required)			
		Mononuclear cell infiltrate - Minimal			
		Vacuolization Cytoplasm - Minimal			
		Thyroid Glands (Required)			
		Follicular cell hypertrophy/height - 3			
		The following Tissues are Examined/Unremarkable:			
		Adrenal Glands	Brain	Epididymis	

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0860	M	9	
			The following Tissues are Examined/Unremarkable:
			Heart Intestine, Large Intestine, Small
			Spleen Stomach Testes
			Thymus
13-0875	M	9	
			Liver (Required)
			Vacuolization Cytoplasm - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands Brain Epididymis
			Heart Intestine, Large Intestine, Small
			Kidneys Spleen Stomach
			Testes Thymus
13-0876	M	9	
			Kidneys (Required)
			Nephropathy - Minimal
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Vacuolization Cytoplasm - Minimal
			Thymus (Required)
			Atrophy - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands Brain Epididymis
			Heart Intestine, Large Intestine, Small
			Spleen Stomach Testes
13-0881	M	9	
			Kidneys (Required) Gross observation (pale kidneys) has no microscopic correlate.

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0881	M	9	
			Kidneys (Required) Gross observation (pale kidneys) has no microscopic correlate.
			Nephropathy - Minimal
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands Brain Epididymis
			Heart Intestine, Large Intestine, Small
			Spleen Stomach Testes
			Thymus
13-0882	M	9	
			Kidneys (Required) Gross observation (pale kidneys) has no microscopic correlate.
			Dilatation - Minimal, Focal, Renal Tubule
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Vacuolization Cytoplasm - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 3
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands Brain Epididymis
			Heart Intestine, Large Intestine, Small
			Spleen Stomach Testes
			Thymus
13-0899	M	9	
			Kidneys (Required)
			Nephropathy - Minimal
			Liver (Required) Gross notation (mildly mottled and dark liver) has no microscopic correlate.
			Mononuclear cell infiltrate - Minimal
			Vacuolization Cytoplasm - Minimal

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0899	M	9	Thyroid Glands (Required) Follicular cell hypertrophy/height - 2 The following Tissues are Examined/Unremarkable: Adrenal Glands Heart Spleen Thymus	Brain Intestine, Large Stomach	Epididymis Intestine, Small Testes
13-0900	M	9	Kidneys (Required) Nephropathy - Minimal Liver (Required) Mononuclear cell infiltrate - Minimal Vacuolization Cytoplasm - Minimal Stomach (Required) Infiltrate, eosinophil - Minimal Thyroid Glands (Required) Follicular cell hypertrophy/height - 3 The following Tissues are Examined/Unremarkable: Adrenal Glands Heart Spleen	Brain Intestine, Large Testes	Epididymis Intestine, Small Thymus
13-0909	M	9	Kidneys (Required) Nephropathy - Minimal Liver (Required) Mononuclear cell infiltrate - Minimal Vacuolization Cytoplasm - Minimal Stomach (Required) Infiltrate, eosinophil - Minimal Thyroid Glands (Required)		

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group
13-0909	M	9
Thyroid Glands (Required)		
Follicular cell hypertrophy/height - 2		
The following Tissues are Examined/Unremarkable:		
Adrenal Glands		
Brain		
Epididymis		
Heart		
Intestine, Large		
Intestine, Small		
Spleen		
Testes		
Thymus		
13-0910	M	9
Liver (Required)		
Gross observation (mildly mottled) has no microscopic correlate.		
Mononuclear cell infiltrate - Minimal		
Vacuolization Cytoplasm - Minimal		
Thyroid Glands (Required)		
Follicular cell hypertrophy/height - 2		
The following Tissues are Examined/Unremarkable:		
Adrenal Glands		
Brain		
Epididymis		
Heart		
Intestine, Large		
Intestine, Small		
Kidneys		
Spleen		
Stomach		
Testes		
Thymus		
13-0863	M	10
Intestine, Large (Required)		
Hemorrhage - Minimal		
Inflammation - Minimal, Acute		
Kidneys (Required)		
Mineralization - Minimal		
Necrosis - Moderate, Renal Tubule, Acute		
Liver (Required)		
Mononuclear cell infiltrate - Minimal		
Spleen (Required)		
Red pulp atrophy - Minimal		
White pulp atrophy - Minimal		

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0863	M	10	
		Stomach (Required)	Gross observation (glandular section of stomach has a dark red patch, 5 mm) corresponds to area of epithelial necrosis and hemorrhage.
		Hemorrhage - Minimal	
		Inflammation - Minimal, Acute	
		Necrosis, glandular stomach - Minimal	
		Testes (Required)	
		Degeneration - Minimal, Germinal Epithelium	
		Thymus (Required)	
		Atrophy - Moderate	
		Thyroid Glands (Required)	
		Follicular cell hypertrophy/height - 2	
		Lungs (Non required)	Lungs not saved/trimmed for histologic processing and exam. Gross observation (lungs soft and spongy) cannot be correlated microscopically.
		Lymph Nodes, Mesenteric (Non required)	Gross observation (mesenteric lymph nodes are red) correlates to sinus hemorrhage noted microscopically.
		Atrophy - Minimal	
		Hemorrhage - Moderate, sinus	
		The following Tissues are Examined/Unremarkable:	
		Adrenal Glands	Brain
		Heart	Intestine, Small
			Epididymis
13-0864	M	10	
		Kidneys (Required)	Gross observation (medulla of kidneys red) corresponds to congestion of renal veins in medullary area. Congestion consistent with death and not pathologic.
		Mineralization - Minimal	
		Necrosis - Minimal, Renal Tubule, Acute	
		Liver (Required)	Gross observation (liver - light and dark mottling throughout) due to vascular congestion. Congestion compatible with death and not noted microscopically as a lesion of pathology.
		Spleen (Required)	Gross observation (spleen small) correlates with minimal lymphoid atrophy.
		Red pulp atrophy - Minimal	
		White pulp atrophy - Mild	

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0864	M	10	Stomach (Required) Necrosis, glandular stomach - Minimal Testes (Required) Degeneration - Minimal, Germinal Epithelium Thymus (Required) Atrophy - Moderate Thyroid Glands (Required) Follicular cell hypertrophy/height - 2 The following Tissues are Examined/Unremarkable: Adrenal Glands Heart Liver	Brain Intestine, Large	Epididymis Intestine, Small
13-0885	M	10	Kidneys (Required) Necrosis - Minimal, Renal Tubule, Acute Nephropathy - Minimal Liver (Required) Mononuclear cell infiltrate - Minimal Spleen (Required) Red pulp atrophy - Mild White pulp atrophy - Moderate Stomach (Required) Erosion/ulcer, forestomach - Moderate, Multifocal Inflammation - Mild, Acute Necrosis, glandular stomach - Minimal Testes (Required) Degeneration - Minimal, Germinal Epithelium Thymus (Required) Atrophy - Moderate	Gross observation (several raised nodules, non-glandular) corresponds to multiple erosion/ulcers and intra- and sub-mucosal inflammation noted microscopically.	

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal			
#	Sex	Group	
13-0885	M	10	
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			Lymph Nodes, Mesenteric (Non required)
			Atrophy - Minimal, Lymphoid
			Hemorrhage - Moderate, sinus
			Tongue (Non required)
			Gross observation (mesenteric lymph nodes - red) correlates to moderate sinus hemorrhage.
			Gross observation (2 mm ulceration on tongue) had no microscopic correlate. Mucosa intact on section presented.
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Epididymis
			Intestine, Small
			Tongue
13-0887	M	10	
			Brain (Required)
			Kidneys (Required)
			Gross notation (brain appears hemorrhagic) was due to marked congestion of brain and meningeal blood vessels, consistent with death.
			Gross observation (bilateral dark) has no clear microscopic correlate. Although diffuse hyalin droplets were noted in renal epithelium, it is unlikely that this contributed to a noticable gross discoloration.
			Accumulation Hyalin Droplets - Mild
			Spleen (Required)
			Red pulp atrophy - Moderate
			White pulp atrophy - Marked
			Stomach (Required)
			Gross observation (stomach lining is red) correlates microscopically to minimal hemorrhage as well as substantial congestion (not diagnosed separately).
			Hemorrhage - Minimal
			Infiltrate, eosinophil - Mild
			Necrosis, glandular stomach - Minimal
			Testes (Required)
			Degeneration - Minimal, Germinal Epithelium
			Thymus (Required)
			Atrophy - Marked
			Thyroid Glands (Required)

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group										
13-0887	M	10	<p>Thyroid Glands (Required)</p> <p>Follicular cell hypertrophy/height - 2</p> <p>Lymph Nodes, Mesenteric (Non required) Gross observation (red) correlates to sinus hemorrhage.</p> <p>Atrophy - Minimal, Lymphoid</p> <p>Hemorrhage - Moderate, sinus</p> <p>The following Tissues are Examined/Unremarkable:</p> <table><tr><td>Adrenal Glands</td><td>Brain</td><td>Epididymis</td></tr><tr><td>Heart</td><td>Intestine, Large</td><td>Intestine, Small</td></tr><tr><td>Liver</td><td></td><td></td></tr></table>	Adrenal Glands	Brain	Epididymis	Heart	Intestine, Large	Intestine, Small	Liver		
Adrenal Glands	Brain	Epididymis										
Heart	Intestine, Large	Intestine, Small										
Liver												
13-0888	M	10	<p>Kidneys (Required)</p> <p>Necrosis - Minimal, Renal Tubule, Acute</p> <p>Spleen (Required)</p> <p>Red pulp atrophy - Moderate</p> <p>White pulp atrophy - Marked</p> <p>Stomach (Required) Gross observation (glandular stomach - patches of redness) corresponds to mucosal congestion which overlies areas of epithelial necrosis and inflammation. Congestion not diagnosed separately.</p> <p>Infiltrate, eosinophil - Minimal</p> <p>Necrosis, glandular stomach - Minimal</p> <p>Testes (Required)</p> <p>Degeneration - Minimal, Germinal Epithelium</p> <p>Thymus (Required)</p> <p>Atrophy - Marked</p> <p>Thyroid Glands (Required)</p> <p>Follicular cell hypertrophy/height - 2</p> <p>Lymph Nodes, Mesenteric (Non required) Gross observation (red) due to sinus hemorrhage noted microscopically.</p> <p>Atrophy - Mild, Lymphoid</p> <p>Hemorrhage - Marked, sinus</p> <p>The following Tissues are Examined/Unremarkable:</p> <table><tr><td>Adrenal Glands</td><td>Brain</td><td>Epididymis</td></tr></table>	Adrenal Glands	Brain	Epididymis						
Adrenal Glands	Brain	Epididymis										

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0888	M	10	
			The following Tissues are Examined/Unremarkable:
			Heart Intestine, Large Intestine, Small
			Liver
13-0907	M	10	
			Epididymis (Required)
			Granuloma - Mild, Multifocal
			Kidneys (Required)
			Gross observation (left and right kidney, dark) corresponds to renal tubular droplets and necrosis noted microscopically.
			Accumulation Hyalin Droplets - Mild
			Necrosis - Minimal, Renal Tubule
			Liver (Required)
			Gross notation (dark) has no clear microscopic correlate; hepatocyte necrosis would appear as a pale mottling or foci. Sinusoidal congestion (consistent with death) was noted but not diagnosed as a lesion of pathology.
			Necrosis - Mild, Centrilobular
			Spleen (Required)
			Red pulp atrophy - Moderate
			White pulp atrophy - Moderate
			Stomach (Required)
			Infiltrate, eosinophil - Minimal
			Testes (Required)
			Degeneration - Minimal, Germinal Epithelium
			Thymus (Required)
			Atrophy - Moderate
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 1
			Lymph Nodes, Mesenteric (Non required)
			Gross notation (dark red mesenteric lymph nodes) corresponds to hemorrhage noted microscopically.
			Hemorrhage - Marked, sinus
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands Brain Heart
			Intestine, Large Intestine, Small

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0907	M	10	
13-0908	M	10	
			Brain (Required)
			Gross observation (blood on underside of brain) corresponds to apparent subdural hemorrhage noted microscopically. Lack of cellular response to hemorrhage suggests this may have been agonal.
			Hemorrhage - Mild, Meninges, Acute
			Spleen (Required)
			Red pulp atrophy - Minimal
			White pulp atrophy - Minimal
			Stomach (Required)
			Infiltrate, eosinophil - Minimal
			Thymus (Required)
			Atrophy - Moderate
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 1
			Lymph Nodes, Mesenteric (Non required)
			Gross observation (red mesenteric lymph nodes) corresponds to sinus hemorrhage at micro.
			Hemorrhage - Marked, sinus
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Epididymis
			Heart
			Intestine, Large
			Intestine, Small
			Kidneys
			Liver
			Testes
13-0914	M	10	
			Kidneys (Required)
			Mineralization - Minimal
			Necrosis - Mild, Renal Tubule, Acute
			Liver (Required)
			Gross observation (pale mottled liver) has no microscopic correlate.
			Spleen (Required)
			Red pulp atrophy - Mild
			White pulp atrophy - Mild
			Stomach (Required)
			Gross observation (2 mm, raised white area on glandular stomach) has no microscopic correlation; however, similar-sized area in forestomach has ulcer with inflammation on micro exam.
			Erosion/ulcer, forestomach - Moderate, Focal

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0914	M	10	
			Stomach (Required)
			Gross observation (2 mm, raised white area on glandular stomach) has no microscopic correlation; however, similar-sized area in forestomach has ulcer with inflammation on micro exam.
			Inflammation - Mild, Subacute
			Thymus (Required)
			Atrophy - Mild
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Liver
			Testes
			Epididymis
			Intestine, Small
13-0861	M	11	
			Intestine, Small (Required)
			Duodenum and ileum present to represent small intestine.
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Kidneys
			Liver
			Stomach
			Testes
			Epididymis
			Intestine, Small
			Spleen
			Thymus
13-0862	M	11	
			Adrenal Glands (Required)
			Vacuolization, zona fasciculata - Mild
			Intestine, Small (Required)
			Small intestine represented by ileum section.
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Spleen (Required)
			White pulp atrophy - Minimal
			Testes (Required)
			Degeneration - Minimal, Germinal Epithelium

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0862	M	11	Thymus (Required)		
			Atrophy - Moderate		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 3		
			The following Tissues are Examined/Unremarkable:		
			Brain	Epididymis	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Stomach		
13-0865	M	11	Kidneys (Required)		
			Nephropathy - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Vacuolization Cytoplasm - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Intestine, Small
			Spleen	Stomach	Testes
			Thymus		
13-0866	M	11	Kidneys (Required)		
			Nephropathy - Minimal		
			Liver (Required)	No micro correlate for gross observation (liver - dark).	
			Mononuclear cell infiltrate - Minimal		
			Vacuolization Cytoplasm - Minimal		
			Spleen (Required)	No micro correlate noted for gross observation (spleen - dark).	
			Testes (Required)		
			Degeneration - Minimal, Focal, Rete Testes		

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal			
#	Sex	Group	
13-0866	M	11	
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Epididymis
			Heart
			Intestine, Large
			Intestine, Small
			Spleen
			Stomach
			Thymus
13-0869	M	11	
			Kidneys (Required)
			Nephropathy - Minimal
			Liver (Required)
			No micro correlate for gross observation (liver - mildly mottled).
			Mononuclear cell infiltrate - Minimal
			Vacuolization Cytoplasm - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Epididymis
			Heart
			Intestine, Large
			Intestine, Small
			Spleen
			Stomach
			Testes
13-0870	M	11	
			Kidneys (Required)
			No micro correlate for gross notation (pale kidneys).
			Nephropathy - Minimal
			Liver (Required)
			Gross observation (liver, mildly mottled) has no microscopic correlate. Focal hepatocyte necrosis was observed microscopically, but would be most likely discernable grossly as a "focus" and not a more disseminated "mottling."
			Mononuclear cell infiltrate - Minimal
			Necrosis - Minimal, Hepatocyte
			Vacuolization Cytoplasm - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0870	M	11	
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Epididymis
			Heart
			Intestine, Large
			Intestine, Small
			Spleen
			Stomach
			Testes
			Thymus
13-0889	M	11	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Epididymis
			Heart
			Intestine, Large
			Intestine, Small
			Kidneys
			Spleen
			Stomach
			Testes
			Thymus
13-0890	M	11	
			Kidneys (Required)
			Nephropathy - Minimal
			Liver (Required)
			Gross observation (liver mildly mottled) had no microscopic correlate.
			Mononuclear cell infiltrate - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Epididymis
			Heart
			Intestine, Large
			Intestine, Small
			Spleen
			Stomach
			Testes
			Thymus
13-0911	M	11	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0911	M	11	Liver (Required)		
			Vacuolization Cytoplasm - Minimal		
			Stomach (Required)		
			Infiltrate, eosinophil - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Intestine, Small
			Kidneys	Spleen	Testes
			Thymus		
13-0912	M	11	Kidneys (Required)		
			Nephropathy - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Vacuolization Cytoplasm - Minimal		
			Stomach (Required)		
			Infiltrate, eosinophil - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 3		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Intestine, Small
			Spleen	Testes	Thymus
13-0855	M	12	Kidneys (Required)		
			Nephropathy - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0855	M	12	Liver (Required)		
			Vacuolization Cytoplasm - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 3		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Intestine, Small
			Spleen	Stomach	Testes
			Thymus		
13-0856	M	12	Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Vacuolization Cytoplasm - Minimal		
			Thymus (Required)		
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Intestine, Small
			Kidneys	Spleen	Stomach
			Testes		
13-0873	M	12	Intestine, Small (Required)	Jejunum and ileum sections presented for micro review.	
			Kidneys (Required)		
			Nephropathy - Minimal		
			Liver (Required)	Gross observation (dark liver) has no microscopic correlate.	
			Mononuclear cell infiltrate - Minimal		
			Vacuolization Cytoplasm - Minimal		

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0873	M	12	Spleen (Required)	Gross observation (spleen enlarged and dark) due to increased extramedullary hematopoiesis noted microscopically.	
			Extramedullary hematopoiesis, increased - Mild		
			Stomach (Required)	Gross observation (spleen adhered to stomach) has no microscopic correlate or evidence of serosal fibrosis.	
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 4		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Heart	Intestine, Large	Intestine, Small
			Stomach	Testes	Thymus
13-0874	M	12	Heart (Required)		
			Cardiomyopathy - Minimal		
			Intestine, Small (Required)		
			Granuloma, peyer's patch - Minimal		
			Liver (Required)	Gross observation (liver slightly mottled) has no microscopic correlate.	
			Mononuclear cell infiltrate - Minimal		
			Vacuolization Cytoplasm - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Epididymis
			Intestine, Large	Kidneys	Spleen
			Stomach	Testes	Thymus
13-0879	M	12	Kidneys (Required)		
			Lymphocytic infiltrate - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0879	M	12	
			Liver (Required)
			Vacuolization Cytoplasm - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Epididymis
			Heart
			Intestine, Large
			Intestine, Small
			Spleen
			Stomach
			Testes
			Thymus
13-0880	M	12	
			Brain (Required)
			Gross notation (hematoma under skull - no evidence of damage to brain) has no microscopic correlate and was interpreted to be agonal/related to necropsy.
			Kidneys (Required)
			Nephropathy - Minimal
			Liver (Required)
			Gross observation (mildly mottled liver) has no micro correlate.
			Mononuclear cell infiltrate - Minimal
			Vacuolization Cytoplasm - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Epididymis
			Heart
			Intestine, Large
			Intestine, Small
			Spleen
			Stomach
			Testes
			Thymus
13-0891	M	12	
			Kidneys (Required)
			Nephropathy - Minimal
			Liver (Required)
			Gross notation (liver mildly mottled) had no microscopic correlate.
			Mononuclear cell infiltrate - Minimal
			Vacuolization Cytoplasm - Minimal

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0891	M	12	
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Epididymis
			Heart
			Intestine, Large
			Intestine, Small
			Spleen
			Stomach
			Testes
			Thymus
13-0892	M	12	
			Liver (Required)
			Gross observation (liver mildly mottled) has no correlate with microscopic appearance. Multifocal mononuclear cell infiltrates and occasional foci of hematopoiesis (not diagnosed as a lesion of pathology) interpreted to be insufficient to be seen grossly.
			Mononuclear cell infiltrate - Minimal
			Vacuolization Cytoplasm - Minimal
			Thymus (Required)
			Atrophy - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Epididymis
			Heart
			Intestine, Large
			Intestine, Small
			Kidneys
			Spleen
			Stomach
			Testes
13-0901	M	12	
			Liver (Required)
			Gross notation (mildly mottled liver) has no microscopic correlation.
			Mononuclear cell infiltrate - Minimal
			Vacuolization Cytoplasm - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Epididymis

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0901	M	12	
			The following Tissues are Examined/Unremarkable:
			Heart Intestine, Large Intestine, Small
			Kidneys Spleen Stomach
			Testes Thymus
13-0902	M	12	
			Liver (Required) Gross notation (mildly mottled liver) has no microscopic correlate.
			Mononuclear cell infiltrate - Minimal
			Vacuolization Cytoplasm - Minimal
			Stomach (Required)
			Infiltrate, eosinophil - Minimal
			Testes (Required)
			Degeneration - Minimal, Germinal Epithelium
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 3
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands Brain Epididymis
			Heart Intestine, Large Intestine, Small
			Kidneys Spleen Thymus
13-0801	F	1	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Ovaries (Required) Only one ovary on slide.
			Thymus (Required)
			Epithelial cell hyperplasia - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			Uterus (Required) Gross notation (mild hydro-uterus) corresponds to microscopic diagnosis of dilation.
			Dilation - Minimal
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands Brain Heart

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0801	F	1	The following Tissues are Examined/Unremarkable:		
			Intestine, Large	Intestine, Small	Kidneys
			Ovaries	Spleen	Stomach
13-0802	F	1			
			Kidneys (Required)		
			Mineralization - Minimal		
			Ovaries (Required)		
			Thymus (Required)		
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 1		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Liver
			Ovaries	Spleen	Stomach
			Uterus		
13-0803	F	1			
			Kidneys (Required)		
			Dilated pelvis - Minimal, Unilateral		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Ovaries (Required)		
			Stomach (Required)		
			Infiltrate, eosinophil - Minimal		
			Thymus (Required)		
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			Uterus (Required)		
			Dilation - Minimal		

The following Tissues are Examined/Unremarkable:

Intestine, Large

Intestine, Small

Kidneys

Ovaries

Spleen

Stomach

Kidneys (Required)

Mineralization - Minimal

Ovaries (Required)

Only one ovary presented on slide for review.

Thymus (Required)

Atrophy - Minimal

Thyroid Glands (Required)

Follicular cell hypertrophy/height - 1

The following Tissues are Examined/Unremarkable:

Adrenal Glands

Brain

Heart

Intestine, Large

Intestine, Small

Liver

Ovaries

Spleen

Stomach

Uterus

Kidneys (Required)

Dilated pelvis - Minimal, Unilateral

Liver (Required)

Mononuclear cell infiltrate - Minimal

Ovaries (Required)

Only one ovary presented on slide for review.

Stomach (Required)

Infiltrate, eosinophil - Minimal

Thymus (Required)

Atrophy - Minimal

Thyroid Glands (Required)

Follicular cell hypertrophy/height - 2

Uterus (Required)

Gross notation (hydro-uterus) correlates with micro diagnosis of dilation.

Dilation - Minimal

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group													
13-0803	F	1	<p>The following Tissues are Examined/Unremarkable:</p> <table><tr><td>Adrenal Glands</td><td>Brain</td><td>Heart</td></tr><tr><td>Intestine, Large</td><td>Intestine, Small</td><td>Ovaries</td></tr><tr><td>Spleen</td><td></td><td></td></tr></table>	Adrenal Glands	Brain	Heart	Intestine, Large	Intestine, Small	Ovaries	Spleen					
Adrenal Glands	Brain	Heart													
Intestine, Large	Intestine, Small	Ovaries													
Spleen															
13-0804	F	1	<p>Liver (Required) Mononuclear cell infiltrate - Minimal Ovaries (Required) Only one ovary presented on slide for review. Stomach (Required) Infiltrate, eosinophil - Minimal Thyroid Glands (Required) Follicular cell hypertrophy/height - 1 The following Tissues are Examined/Unremarkable:</p> <table><tr><td>Adrenal Glands</td><td>Brain</td><td>Heart</td></tr><tr><td>Intestine, Large</td><td>Intestine, Small</td><td>Kidneys</td></tr><tr><td>Ovaries</td><td>Spleen</td><td>Thymus</td></tr><tr><td>Uterus</td><td></td><td></td></tr></table>	Adrenal Glands	Brain	Heart	Intestine, Large	Intestine, Small	Kidneys	Ovaries	Spleen	Thymus	Uterus		
Adrenal Glands	Brain	Heart													
Intestine, Large	Intestine, Small	Kidneys													
Ovaries	Spleen	Thymus													
Uterus															
13-0829	F	1	<p>Liver (Required) Gross notation (liver slightly mottled) has no microscopic correlate. Ovaries (Required) Only one ovary on slide for review. Stomach (Required) Infiltrate, eosinophil - Minimal Thyroid Glands (Required) Follicular cell hypertrophy/height - 2 Uterus (Required) Dilation - Minimal The following Tissues are Examined/Unremarkable:</p> <table><tr><td>Adrenal Glands</td><td>Brain</td><td>Heart</td></tr><tr><td>Intestine, Large</td><td>Intestine, Small</td><td>Kidneys</td></tr><tr><td>Liver</td><td>Ovaries</td><td>Spleen</td></tr></table>	Adrenal Glands	Brain	Heart	Intestine, Large	Intestine, Small	Kidneys	Liver	Ovaries	Spleen			
Adrenal Glands	Brain	Heart													
Intestine, Large	Intestine, Small	Kidneys													
Liver	Ovaries	Spleen													

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0829	F	1	The following Tissues are Examined/Unremarkable:		
			Thymus		
13-0830	F	1	Gross observation (liver slightly mottled) has no microscopic correlate.		
			Liver (Required)		
			Ovaries (Required)		Only one ovary on slide for review.
			Thymus (Required)		
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			Uterus (Required)		
			Endometrial hyperplasia - Minimal		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Liver	Ovaries	Spleen
			Stomach		
13-0837	F	1	Gross observation (liver slightly mottled) has no microscopic correlate.		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 1		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Ovaries	Spleen	Stomach
			Thymus	Uterus	
13-0838	F	1	Gross observation (liver slightly mottled) has no microscopic correlate.		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Ovaries (Required)		Only one ovary present on slide for review.

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal		
#	Sex	Group
13-0838	F	1
	Thyroid Glands (Required)	
	Follicular cell hypertrophy/height - 2	
	The following Tissues are Examined/Unremarkable:	
	Adrenal Glands	Brain
	Intestine, Large	Intestine, Small
	Ovaries	Spleen
	Thymus	Uterus
13-0849	F	1
	Kidneys (Required)	
	Mineralization - Minimal	
	Nephropathy - Minimal	
	Ovaries (Required)	One ovary not present for review.
	Thyroid Glands (Required)	
	Follicular cell hypertrophy/height - 2	
	Uterus (Required)	
	Dilation - Minimal	
	The following Tissues are Examined/Unremarkable:	
	Adrenal Glands	Brain
	Intestine, Large	Intestine, Small
	Ovaries	Spleen
	Thymus	
13-0850	F	1
	Adrenal Glands (Required)	Only one adrenal on slide for review.
	Liver (Required)	
	Mononuclear cell infiltrate - Minimal	
	Ovaries (Required)	Only one ovary on slide for review.
	Thyroid Glands (Required)	
	Follicular cell hypertrophy/height - 2	
	The following Tissues are Examined/Unremarkable:	
	Adrenal Glands	Brain
		Heart

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0850	F	1	The following Tissues are Examined/Unremarkable:		
			Intestine, Large	Intestine, Small	Kidneys
			Ovaries	Spleen	Stomach
			Thymus	Uterus	
13-0799	F	2	Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Vacuolization Cytoplasm - Minimal		
			Ovaries (Required)	Only one ovary on slide for review.	
			Stomach (Required)		
			Infiltrate, eosinophil - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Ovaries	Spleen	Thymus
			Uterus		
13-0800	F	2	Kidneys (Required)		
			Mineralization - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Ovaries (Required)	Only one ovary presented on slide.	
			Stomach (Required)		
			Infiltrate, eosinophil - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			Uterus (Required)	Gross notation (mild hydro-uterus) corresponds to dilation coded microscopically.	
			Dilation - Minimal		

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal			
#	Sex	Group	
13-0800	F	2	
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Ovaries
			Spleen
			Thymus
13-0811	F	2	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Ovaries (Required)
			Only one ovary present on slide for review.
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 1
			Uterus (Required)
			Gross observation (hydro-uterus) correlates with minimal dilation at micro exam.
			Dilation - Minimal
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Kidneys
			Ovaries
			Spleen
			Stomach
			Thymus
13-0812	F	2	
			Liver (Required)
			Gross observation (liver mildly mottled) has no microscopic correlate.
			Mononuclear cell infiltrate - Minimal
			Vacuolization Cytoplasm - Minimal
			Ovaries (Required)
			Only one ovary presented on slide.
			Thymus (Required)
			Atrophy - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Kidneys
			Ovaries
			Spleen
			Stomach

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0812	F	2	The following Tissues are Examined/Unremarkable:		
			Uterus		
13-0815	F	2	Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Ovaries (Required)	Only one ovary on slide for review.	
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 1		
			Uterus (Required)	Gross observation (mild hydro-uterus) correlates with minimal dilation.	
			Dilation - Minimal		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Ovaries	Spleen	Stomach
			Thymus		
13-0816	F	2	Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Ovaries (Required)	Only one ovary present for review.	
			Thymus (Required)		
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Ovaries	Spleen	Stomach
			Uterus		
13-0821	F	2	Liver (Required)		

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal			
#	Sex	Group	
13-0821	F	2	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Ovaries (Required) Only one ovary present on slide for review.
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands Brain Heart
			Intestine, Large Intestine, Small Kidneys
			Ovaries Spleen Stomach
			Thymus Uterus
13-0822	F	2	
			Ovaries (Required) Only one ovary present on slide for review.
			Spleen (Required) Gross observation (5 mm constriction) correlates to an anatomic deformity at micro exam.
			Deformity - Mild
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			Uterus (Required)
			Dilation - Minimal
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands Brain Heart
			Intestine, Large Intestine, Small Kidneys
			Liver Ovaries Stomach
			Thymus
13-0831	F	2	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Ovaries (Required) Only one ovary on slide for review.
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0831	F	2	The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Ovaries	Spleen	Stomach
			Thymus	Uterus	
13-0832	F	2	Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Ovaries (Required)	Only one ovary on slide for review.	
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Ovaries	Spleen	Stomach
			Thymus	Uterus	
13-0807	F	3	Kidneys (Required)		
			Mineralization - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Vacuolization Cytoplasm - Minimal		
			Ovaries (Required)	Only one ovary on slide for review.	
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Ovaries
			Spleen	Stomach	Thymus
			Uterus		

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0807	F	3	
13-0808	F	3	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Stomach (Required)
			Infiltrate, eosinophil - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			Lungs (Non required)
			Gross observation (right lung lobe has several 2 mm dark red foci) appears to correlate microscopically with (1) a large, congested blood vessel and (2) area of RBC extravasation due to tissue handling. Lung tissue proper is normal.
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Kidneys
			Ovaries
			Spleen
			Thymus
			Uterus
			Lungs
13-0817	F	3	
			Kidneys (Required)
			Nephropathy - Minimal
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			Uterus (Required)
			Gross observation (hydro-uterus) correlates with very minimal dilation.
			Dilation - Minimal
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Ovaries
			Spleen
			Stomach
			Thymus
13-0818	F	3	
			Liver (Required)
			Gross observation (liver mildly mottled) has no microscopic correlate.

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0818	F	3	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Vacuolization Cytoplasm - Minimal
			Spleen (Required)
			White pulp atrophy - Mild
			Thymus (Required)
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Intestine, Large
			Ovaries
			Brain
			Intestine, Small
			Stomach
			Heart
			Kidneys
			Uterus
13-0819	F	3	
			Kidneys (Required)
			Mineralization - Minimal
			Stomach (Required)
			Infiltrate, eosinophil - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			Uterus (Required)
			Dilation - Minimal
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Intestine, Large
			Ovaries
			Brain
			Intestine, Small
			Spleen
			Heart
			Liver
			Thymus
13-0820	F	3	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Stomach (Required)
			Infiltrate, eosinophil - Minimal

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0820	F	3			
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Ovaries	Spleen	Thymus
			Uterus		
13-0845	F	3			
			Kidneys (Required)		
			Nephropathy - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Spleen (Required)	Gross notation (tip of spleen missing) has no microscopic correlate.	Section of spleen presented is within normal limits.
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			Uterus (Required)		
			Dilation - Minimal		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Ovaries
			Spleen	Stomach	Thymus
13-0846	F	3			
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Liver	Ovaries	Spleen
			Stomach	Thymus	Uterus

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal					
#	Sex	Group			
13-0846	F	3			
13-0847	F	3			
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 1		
			Uterus (Required)		
			Endometrial hyperplasia - Minimal		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Liver	Ovaries	Spleen
			Stomach	Thymus	
13-0848	F	3			
			Kidneys (Required)		
			Mineralization - Minimal		
			Liver (Required)		
			Gross observation (liver slightly mottled) has no microscopic correlate.		
			Mononuclear cell infiltrate - Minimal		
			Thymus (Required)		
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 1		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Ovaries
			Spleen	Stomach	Uterus
13-0797	F	4			
			Kidneys (Required)		
			Nephropathy - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Stomach (Required)		
			Infiltrate, eosinophil - Minimal		

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal			
#	Sex	Group	
13-0797	F	4	
			Thymus (Required)
			Atrophy - Minimal
			Thyroid Glands (Required)
			Only one thyroid lobe presented on slide.
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Ovaries
			Spleen
			Uterus
13-0798	F	4	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Stomach (Required)
			Infiltrate, eosinophil - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Kidneys
			Ovaries
			Spleen
			Thymus
			Uterus
13-0809	F	4	
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 1
			Uterus (Required)
			Gross observation (hydro-uterus) corresponds with very slight dilation noted microscopically.
			Dilation - Minimal
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Kidneys
			Liver
			Ovaries
			Spleen
			Stomach
			Thymus

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0809	F	4			
13-0810	F	4			
			Kidneys (Required)		
			Mineralization - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Stomach (Required)		
			Infiltrate, eosinophil - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Ovaries
			Spleen	Thymus	Uterus
13-0827	F	4			
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 1		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Ovaries	Spleen	Stomach
			Thymus	Uterus	
13-0828	F	4			
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			Uterus (Required)		
			Dilation - Minimal		

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group													
13-0828	F	4	<p>The following Tissues are Examined/Unremarkable:</p> <table><tr><td>Adrenal Glands</td><td>Brain</td><td>Heart</td></tr><tr><td>Intestine, Large</td><td>Intestine, Small</td><td>Kidneys</td></tr><tr><td>Ovaries</td><td>Spleen</td><td>Stomach</td></tr><tr><td>Thymus</td><td></td><td></td></tr></table>	Adrenal Glands	Brain	Heart	Intestine, Large	Intestine, Small	Kidneys	Ovaries	Spleen	Stomach	Thymus		
Adrenal Glands	Brain	Heart													
Intestine, Large	Intestine, Small	Kidneys													
Ovaries	Spleen	Stomach													
Thymus															
13-0851	F	4	<p>Intestine, Small (Required)</p> <p>Mineralization, peyer's patch - Mild</p> <p>Thyroid Glands (Required)</p> <p>Follicular cell hypertrophy/height - 2</p> <p>Uterus (Required)</p> <p>Endometrial hyperplasia - Minimal</p> <p>The following Tissues are Examined/Unremarkable:</p> <table><tr><td>Adrenal Glands</td><td>Brain</td><td>Heart</td></tr><tr><td>Intestine, Large</td><td>Kidneys</td><td>Liver</td></tr><tr><td>Ovaries</td><td>Spleen</td><td>Stomach</td></tr><tr><td>Thymus</td><td></td><td></td></tr></table>	Adrenal Glands	Brain	Heart	Intestine, Large	Kidneys	Liver	Ovaries	Spleen	Stomach	Thymus		
Adrenal Glands	Brain	Heart													
Intestine, Large	Kidneys	Liver													
Ovaries	Spleen	Stomach													
Thymus															
13-0852	F	4	<p>Liver (Required)</p> <p>Mononuclear cell infiltrate - Minimal</p> <p>Thyroid Glands (Required)</p> <p>Follicular cell hypertrophy/height - 1</p> <p>The following Tissues are Examined/Unremarkable:</p> <table><tr><td>Adrenal Glands</td><td>Brain</td><td>Heart</td></tr><tr><td>Intestine, Large</td><td>Intestine, Small</td><td>Kidneys</td></tr><tr><td>Ovaries</td><td>Spleen</td><td>Stomach</td></tr><tr><td>Thymus</td><td>Uterus</td><td></td></tr></table>	Adrenal Glands	Brain	Heart	Intestine, Large	Intestine, Small	Kidneys	Ovaries	Spleen	Stomach	Thymus	Uterus	
Adrenal Glands	Brain	Heart													
Intestine, Large	Intestine, Small	Kidneys													
Ovaries	Spleen	Stomach													
Thymus	Uterus														
13-0853	F	4	<p>Ovaries (Required)</p> <p>Stomach (Required)</p> <p>Only one ovary on slide for review.</p>												

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0853	F	4	Stomach (Required)		
			Infiltrate, eosinophil - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Liver	Ovaries	Spleen
			Thymus	Uterus	
13-0854	F	4	Thymus (Required)		
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			Uterus (Required)		
			Endometrial hyperplasia - Minimal		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Liver	Ovaries	Spleen
			Stomach		
13-0823	F	5	Kidneys (Required)		
			Mineralization - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Stomach (Required)		
			Infiltrate, eosinophil - Minimal		
			Thymus (Required)		
			Atrophy - Minimal		

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BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal			
#	Sex	Group	
13-0823	F	5	
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Ovaries
			Spleen
			Uterus
13-0824	F	5	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Stomach (Required)
			Infiltrate, eosinophil - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			Uterus (Required)
			Gross notation (mild hydro-uterus) correlates with dilation noted microscopically.
			Dilation - Minimal
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Kidneys
			Ovaries
			Spleen
			Thymus
13-0833	F	5	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			Uterus (Required)
			Gross observation (mild hydro-uterus) correlates with dilation noted microscopically.
			Dilation - Minimal
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Kidneys
			Ovaries
			Spleen
			Stomach

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0833	F	5	The following Tissues are Examined/Unremarkable:		
			Thymus		
13-0834	F	5	Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Stomach (Required)		
			Infiltrate, eosinophil - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys
			Ovaries	Spleen	Thymus
			Uterus		
13-0835	F	5	Kidneys (Required)		
			Mineralization - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Stomach (Required)		
			Infiltrate, eosinophil - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 2		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Ovaries
			Spleen	Thymus	Uterus
13-0836	F	5	Kidneys (Required)		
			Mineralization - Minimal		

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0836	F	5	
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Stomach (Required)
			Infiltrate, eosinophil - Minimal
			Thymus (Required)
			Atrophy - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Ovaries
			Spleen
			Uterus
13-0841	F	5	
			Liver (Required)
			Gross notation (liver slightly mottled and pale) has no microscopic correlate.
			Stomach (Required)
			Infiltrate, eosinophil - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			Uterus (Required)
			Gross observation (mild hydro-uterus) correlates with minimal endometrial hyperplasia on micro exam.
			Hyperplasia consistent with physiologic cycling.
			Endometrial hyperplasia - Minimal
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Brain
			Heart
			Intestine, Large
			Intestine, Small
			Kidneys
			Liver
			Ovaries
			Spleen
			Thymus
13-0842	F	5	
			Stomach (Required)
			Infiltrate, eosinophil - Minimal
			Thyroid Glands (Required)

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0842	F	5	Thyroid Glands (Required) Follicular cell hypertrophy/height - 2 Uterus (Required) Dilation - Minimal The following Tissues are Examined/Unremarkable: Adrenal Glands Intestine, Large Liver Thymus	Brain Intestine, Small Ovaries	Heart Kidneys Spleen
13-0843	F	5	Stomach (Required) Infiltrate, eosinophil - Minimal Thyroid Glands (Required) Follicular cell hypertrophy/height - 2 The following Tissues are Examined/Unremarkable: Adrenal Glands Intestine, Large Liver Thymus	Brain Intestine, Small Ovaries Uterus	Heart Kidneys Spleen
13-0844	F	5	Kidneys (Required) Mineralization - Minimal Thyroid Glands (Required) Follicular cell hypertrophy/height - 2 Uterus (Required) Dilation - Minimal The following Tissues are Examined/Unremarkable: Adrenal Glands Intestine, Large Ovaries	Gross observation (mild hydro-uterus) correlates with dilation noted at micro exam. Brain Intestine, Small Spleen	Heart Liver Stomach

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0844	F	5	The following Tissues are Examined/Unremarkable: Thymus
13-0795	F	6	Liver (Required) Mononuclear cell infiltrate - Minimal Ovaries (Required) Only one ovary on slide. Thyroid Glands (Required) Follicular cell hypertrophy/height - 2 Uterus (Required) Gross notation (mild hydro-uterus) corresponds to very minimal dilation of the lumen. Minimal dilation is consistent with phase of uterine cycle. Dilation - Minimal The following Tissues are Examined/Unremarkable: Adrenal Glands Brain Heart Intestine, Large Intestine, Small Kidneys Ovaries Spleen Stomach Thymus
13-0796	F	6	Intestine, Small (Required) Mineralization, peyer's patch - Mild Kidneys (Required) Accumulation Hyalin Droplets - Minimal Ovaries (Required) Only one ovary presented on slide. Spleen (Required) White pulp atrophy - Minimal Stomach (Required) Gross observation (small red areas/patches) corresponds to mucosal congestion and hemorrhage on micro exam. Hemorrhage - Minimal Thymus (Required) Atrophy - Moderate Thyroid Glands (Required) Only one thyroid lobe presented on slide.

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal			
#	Sex	Group	
13-0796	F	6	
			Thyroid Glands (Required) Only one thyroid lobe presented on slide.
			Follicular cell hypertrophy/height - 2
			Uterus (Required) Gross observation (hydrometrios) correlates with minimal dilation noted microscopically.
			Dilation - Minimal
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands Brain Heart
			Intestine, Large Liver Ovaries
13-0805	F	6	
			Kidneys (Required)
			Necrosis - Mild, Renal Tubule, Acute
			Ovaries (Required) Only one ovary present on slide for review.
			Spleen (Required)
			Red pulp atrophy - Mild
			White pulp atrophy - Moderate
			Stomach (Required) Gross observation (2 mm diameter red patch, glandular) correlates with mucosal hemorrhage noted at micro exam.
			Hemorrhage - Moderate
			Inflammation - Minimal, Acute
			Necrosis, glandular stomach - Minimal
			Thymus (Required)
			Atrophy - Marked
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 1
			Lymph Nodes, Mesenteric (Non required) Gross observation (mesenteric lymph nodes - red) correlates to sinus hemorrhage seen microscopically.
			Hemorrhage - Mild, sinus
			Infiltrate, histiocyte - Moderate, sinus
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands Brain Heart
			Intestine, Large Intestine, Small Liver
			Ovaries Uterus

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group	
13-0805	F	6	
13-0806	F	6	
			Kidneys (Required)
			Necrosis - Minimal, Renal Tubule, Acute
			Nephropathy - Minimal
			Liver (Required)
			Mononuclear cell infiltrate - Minimal
			Ovaries (Required)
			Thymus (Required)
			Atrophy - Mild
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 2
			The following Tissues are Examined/Unremarkable:
			Adrenal Glands
			Intestine, Large
			Spleen
			Brain
			Intestine, Small
			Stomach
			Heart
			Ovaries
			Uterus
13-0813	F	6	
			Adrenal Glands (Required)
			Intestine, Large (Required)
			Inflammation - Minimal, Subacute
			Liver (Required)
			Ovaries (Required)
			Stomach (Required)
			Erosion/ulcer, forestomach - Minimal
			Inflammation - Minimal, Subacute
			Thymus (Required)
			Atrophy - Minimal
			Thyroid Glands (Required)
			Follicular cell hypertrophy/height - 1
			Uterus (Required)

Only one ovary presented on slide.

Gross observation (right adrenal in fluid-filled cyst) has no micro correlation (no cyst or mesenteric cyst found).

Gross notation (liver slightly mottled) has no microscopic abnormality to correlate.
Only one ovary on slide.

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0813	F	6	Uterus (Required) Dilation - Minimal The following Tissues are Examined/Unremarkable: Adrenal Glands Intestine, Small Ovaries	Brain Kidneys Spleen	Heart Liver
13-0814	F	6	Liver (Required) Mononuclear cell infiltrate - Minimal Ovaries (Required) Thymus (Required) Atrophy - Minimal Thyroid Glands (Required) Follicular cell hypertrophy/height - 2 The following Tissues are Examined/Unremarkable: Adrenal Glands Intestine, Large Ovaries Uterus	Only one ovary on slide for review. Brain Intestine, Small Spleen	Heart Kidneys Stomach
13-0825	F	6	Kidneys (Required) Accumulation Hyalin Droplets - Mild Necrosis - Mild, Renal Tubule, Acute Liver (Required) Ovaries (Required) Spleen (Required) Red pulp atrophy - Moderate White pulp atrophy - Moderate	Gross observation (medulla of kidney has red outer rim) correlates with acute tubular necrosis with vascular congestion (congestion not diagnosed separately). Gross notation of pale liver has no microscopic correlate. Only one ovary presented on slide for review. Gross observation (small spleen) correlates with both red and white pulp atrophy, as noted microscopically.	

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Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0825	F	6	Stomach (Required)	Gross notation (focal red area in glandular stomach with overlying black material) correlates with mucosal necrosis noted microscopically.	
			Infiltrate, eosinophil - Minimal		
			Necrosis, glandular stomach - Minimal		
			Thymus (Required)		
			Atrophy - Moderate		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 1		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Liver
			Ovaries	Uterus	
13-0826	F	6	Heart (Required)		
			Cardiomyopathy - Minimal		
			Liver (Required)		
			Mononuclear cell infiltrate - Minimal		
			Ovaries (Required)	Only one ovary on slide for review.	
			Spleen (Required)		
			White pulp atrophy - Minimal		
			Thymus (Required)		
			Atrophy - Moderate		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 1		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Intestine, Large
			Intestine, Small	Kidneys	Ovaries
			Stomach	Uterus	
13-0839	F	6	Intestine, Large (Required)		

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal #	Sex	Group			
13-0839	F	6			
			Intestine, Large (Required)		
			Mononuclear cell infiltrate, muscle wall - Mild		
			Kidneys (Required)		
			Nephropathy - Minimal		
			Ovaries (Required)	Only one ovary present on slide for review.	
			Spleen (Required)		
			Red pulp atrophy - Mild		
			White pulp atrophy - Mild		
			Thymus (Required)		
			Atrophy - Mild		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 1		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Small	Liver	Ovaries
			Stomach	Uterus	
13-0840	F	6			
			Liver (Required)		
			Necrosis - Minimal, Focal, Hepatocyte, Acute		
			Ovaries (Required)	Only one ovary on slide for review.	
			Spleen (Required)		
			Red pulp atrophy - Minimal		
			White pulp atrophy - Minimal		
			Thymus (Required)		
			Atrophy - Minimal		
			Thyroid Glands (Required)		
			Follicular cell hypertrophy/height - 1		
			The following Tissues are Examined/Unremarkable:		
			Adrenal Glands	Brain	Heart
			Intestine, Large	Intestine, Small	Kidneys

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Animal					
#	Sex	Group			
13-0840	F	6			
			The following Tissues are Examined/Unremarkable:		
			Ovaries	Stomach	Uterus

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Battelle Toxicology Columbus

Study: 12918

BBRC Rat/Unspecified

Acute (1-14 days)/Oral

Report Selections

Report generated by

Study Animal Number

Denise Mounts

13-0867,13-0868,13-0877,13-0878,13-0883,13-0884,13-0897,13-0898,13-0903,13-0904,13-0857,13-0858,13-0872,13-0893,13-0894,13-0895,13-0896,13-0905,13-0906,13-0859,13-0860,13-0875,13-0876,13-0881,13-0882,13-0899,13-0900,13-0909,13-0910,13-0863,13-0864,13-0885,13-0887,13-0888,13-0907,13-0908,13-0914,13-0861,13-0862,13-0865,13-0866,13-0869,13-0870,13-0889,13-0890,13-0911,13-0912,13-0855,13-0856,13-0873,13-0874,13-0879,13-0880,13-0891,13-0892,13-0901,13-0902,13-0801,13-0802,13-0803,13-0804,13-0829,13-0830,13-0837,13-0838,13-0849,13-0850,13-0799,13-0800,13-0811,13-0812,13-0815,13-0816,13-0821,13-0822,13-0831,13-0832,13-0807,13-0808,13-0817,13-0818,13-0819,13-0820,13-0845,13-0846,13-0847,13-0848,13-0797,13-0798,13-0809,13-0810,13-0827,13-0828,13-0851,13-0852,13-0853,13-0854,13-0823,13-0824,13-0833,13-0834,13-0835,13-0836,13-0841,13-0842,13-0843,13-0844,13-0795,13-0796,13-0805,13-0806,13-0813,13-0814,13-0825,13-0826,13-0839,13-0840

ANNEX B: Anatomic Pathology Narrative – Effects of Acute Oral 5-Aminotetrazole (5-At) Exposure to Rats (*Rattus Norvegicus*)

ANATOMIC PATHOLOGY NARRATIVE

**EFFECTS OF ACUTE ORAL 5-AMINOTETRAZOLE (5-AT) EXPOSURE TO RATS
(*RATTUS NORVEGICUS*)**

Battelle Study No. 12918B
USAPHC Study No. 30-13-07-10

July 29, 2014

Prepared By:



Anthony J. Skowronek, D.V.M., Ph.D.
Diplomate, A.C.V.P.
Study Pathologist



Date

Approved By:



Allen W. Singer, D.V.M., D.A.B.T.
Diplomate, A.C.V.P.
Technical Review



Date

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COMPLIANCE STATEMENT

This pathology investigation was conducted in a manner consistent with the principles of the United States Environmental Protection Agency (USEPA) Good Laboratory Practice regulations of the Toxic Substances Control Act (TSCA), as detailed in 40 CFR Part 792, plus amendments. Data were collected using the Next Generation PATH/TOX SYSTEM, V. 1.7.2 Build 37 (Xybion Medical Systems Corporation, Morris Plains, NJ), which has been validated for use on regulated studies by Battelle, Columbus, OH.



Anthony J. Skowronek, D.V.M., Ph.D.
Diplomate, A.C.V.P.
Principal Investigator

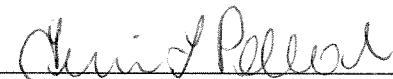



Date

QUALITY ASSURANCE STATEMENT

This study was inspected by the Quality Assurance Unit and reports were submitted to the study director and management as follows:

Phase Inspected	Date Inspected	Date Reported to Battelle Principal Investigator and Management	Date of Report to Offsite Study Director and Management
Slide staining	12/16/2013	12/16/2013	12/16/2013
Audit study file	4/18/2014	4/18/2014	4/18/2014
Audit draft anatomic pathology narrative	4/18/2014	4/18/2014	4/18/2014
Audit final anatomic pathology narrative	7/23/2014	7/23/2014	7/23/2014


Quality Assurance Unit


Date

1.0 NECROPSY

The purpose of this study was to assess the toxicity of 5-aminotetrazole (5-AT). 5-AT is being considered as a replacement for perchlorate as an explosive modifier.

The in-life portion of this study was conducted at the Toxicology Directorate, U.S. Army Public Health Command at Aberdeen Proving Ground (Edgewood Area), MD, 21010-5403, under approved protocol 30-13-07-01. The sponsoring agency was the U.S. Army Research Development and Engineering Command, Environmental Acquisition and Logistics Sustainment Program, Aberdeen Proving Ground, MD, 21010.

As defined in the protocol, 84 rats were divided into six exposure groups and one control group. Rats were orally administered 5-AT for up to 14 days at escalating doses (summarized in Table 1) and then necropsied.

Table 1. Experimental Design

Dose Group	Males	Females
Control (0 mg/kg/day)	6	6
22 mg/kg/day	6	6
44 mg/kg/day	6	6
88 mg/kg/day	6	6
175 mg/kg/day	6	6
310 mg/kg/day	6	6
621 mg/kg/day	6	6

Organ weights were recorded manually on the individual animal *Toxicology Directorate Necropsy Report* for adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, spleen, testes, thymus, and uterus.

For this study, selected tissues (liver, kidney, spleen and heart) along with copies of the individual animal Necropsy Reports (CHPPM Form 333-E, Sep 97) from the control group (0 mg/kg/day, male and female, designated Group 1 in the Tables 2 through 5) and high dose group (621 mg/kg/day, males and females, designated Group 2 in the Tables 2 through 5) were submitted to Battelle for routine processing to slides (stained with hematoxylin and eosin) and histopathologic examination.

2.0 PATHOLOGY

2.1 Necropsy

Based on data presented on each Necropsy Report, all rats submitted herein survived their 14 days of dosing. Per protocol, a complete necropsy was performed on all

rats, with organ weights collected on all submitted rats. Organ weight data, as recorded on the Necropsy Reports, were not statistically analyzed by the undersigned. A visual comparison of treated rat organ weight data with those from the same-sex controls was made; organ weight changes were interpreted to be within the biologic variation expected in young rats and deemed unrelated to 5-AT administration.

There were no gross (macroscopic) findings interpreted as related to 5-AT administration (Table 2). Gross findings in the liver (noted as “liver, mottled” in 13-0969, 13-0970, 13-0983, 13-0984, and 13-1019) correlated microscopically to hepatocyte cytoplasm vacuolization (with exception to 13-0984 and 13-1019; each with no microscopic correlate). Hepatocyte cytoplasm vacuolization was interpreted as a normal physiologic finding in young rats and deemed unrelated to 5-AT administration.

A few other gross findings were observed at necropsy in various organs (see tables). These tissues were not examined microscopically.

2.2 Histopathology

Sections of liver, kidney, spleen, and heart were trimmed, slides prepared, and submitted for examination by an A.C.V.P. board-certified veterinary pathologist in a “blinded” fashion (i.e., the veterinary pathologist was not aware dose of assignment). All tissues were successfully processed to slides. Diagnoses were entered into the Next Generation PATH/TOX SYSTEM data-management system for table preparation. Following a “blinded” read by the pathologist, individual animal findings were sent to the study director for review followed by “unblinding” the data by revealing dose group assignments. The narrative, discussion, and tables generated herein are reflective of the “unblinded” data. There were no findings in the liver, kidney, spleen, or heart related to 5-AT administration.

Incidence summaries of microscopic observations are presented in Tables 2 (males) and 3 (females). The microscopic incidence tables list average severity for each respective finding. Individual animal gross/microscopic pathology data are presented in Tables 4 (males) and 5 (females).

A variety of non-neoplastic findings were noted in various tissues and were semiquantitatively graded across a theoretical 4-point scale, where Grade 1 (minimal) referred to a minor change of negligible biologic significance or which affected less than 10 percent of the presented tissue area, and Grade 2 (mild) referred to a greater change which affected 10 to 19 percent of the tissue area. Grade 3 (moderate) was scaled to refer to a change of clear biologic relevance and which affected at least 20 percent of the tissue area; and Grade 4 (marked) was scaled for lesions considered to be of maximal morphologic change. There were no Grade 3 or Grade 4 lesions noted microscopically in the tissues submitted.

3.0 CONCLUSIONS

There were no gross, microscopic and/or organ weight findings related to exposure of 5-AT for 14 days to male and female rats at a concentration of 621 mg/kg/day.

4.0 STORAGE OF STUDY MATERIALS AND RECORDS RETENTION

Copies of the Battelle study records and final report will be archived and maintained at or under the direction of Battelle, according to testing facility SOP and EPA requirements. The Pathology specimens archived at Battelle (slides submitted from the USAPHC for examination herein) and study file will be returned to the USAPHC for archival.

Table 2. Incidence Summary of Microscopic Observations with Average Severity – Males, Core Necropsy

Group Legend: 1-1; 2-2			
		Number Observed Per Group	
Tissue/Observation	Group:	1	2
Heart	Number Examined:	6	6
Cardiomyopathy		1	0
	Average Severity:	1.0	0.0
Hyperplasia, Mesothelium, Focal		0	1
	Average Severity:	0.0	2.0
Kidneys	Number Examined:	6	6
Cyst, Tubular		0	1
	Average Severity:	0.0	1.0
Nephropathy		1	2
	Average Severity:	1.0	1.0
Liver	Number Examined:	6	6
Cytoplasm Vacuolization, Hepatocyte		6	5
	Average Severity:	1.3	1.6
Infiltrate, mononuclear cell		5	4
	Average Severity:	1.0	1.0
Spleen	Number Examined:	6	6

Table 3. Incidence Summary of Microscopic Observations with Average Severity – Females, Core Necropsy

Group Legend: 1-1; 2-2			
		Number Observed Per Group	
Tissue/Observation	Group:	1	2
Heart	Number Examined:	6	6
Cardiomyopathy		1	0
	Average Severity:	1.0	0.0
Kidneys	Number Examined:	6	6
Cyst, Tubular		1	0
	Average Severity:	1.0	0.0
Hydronephrosis		1	0
	Average Severity:	1.0	0.0
Nephropathy		1	3
	Average Severity:	1.0	1.0
Liver	Number Examined:	6	6
Cytoplasm Vacuolization, Hepatocyte		6	6
	Average Severity:	1.5	1.2
Infiltrate, mononuclear cell		4	4
	Average Severity:	1.0	1.0
Necrosis, Hepatocyte, Focal		0	1
	Average Severity:	0.0	1.0
Spleen	Number Examined:	6	6

Table 4. Individual Gross and Microscopic Observations – Males

Animal ID: 13-0953			Group: 1
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Heart	No gross observed on tissue.		Cardiomyopathy, Minimal
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Minimal Infiltrate, mononuclear cell, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Kidneys; Spleen

Table 4. Individual Gross and Microscopic Observations – Males (Continued)

Animal ID: 13-0954			Group: 1
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Mild

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 4. Individual Gross and Microscopic Observations – Males (Continued)

Animal ID: 13-0969			Group: 1
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	Discoloration(s), Mottled /Comments: mildly	Correlated	Infiltrate, mononuclear cell, Minimal Cytoplasm Vacuolization, Hepatocyte, Minimal
Testes	Small, Left	Not Correlated	
Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:			
Heart; Kidneys; Spleen			

Table 4. Individual Gross and Microscopic Observations – Males (Continued)

Animal ID: 13-0970			Group: 1
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Kidneys	No gross observed on tissue.		Nephropathy, Minimal
Liver	Discoloration(s), Pale /Comments: mottled, mildly	Correlated	Infiltrate, mononuclear cell, Minimal Cytoplasm Vacuolization, Hepatocyte, Mild
Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:			
Heart; Spleen			

Table 4. Individual Gross and Microscopic Observations – Males (Continued)

Animal ID: 13-0985			Group: 1
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Minimal Infiltrate, mononuclear cell, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 4. Individual Gross and Microscopic Observations – Males (Continued)

Animal ID: 13-0986			Group: 1
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Minimal Infiltrate, mononuclear cell, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 4. Individual Gross and Microscopic Observations – Males (Continued)

Animal ID: 13-0951			Group: 2
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Kidneys	No gross observed on tissue.		Cyst, Tubular, Minimal Nephropathy, Minimal
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Mild Infiltrate, mononuclear cell, Minimal
Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:			
Heart; Spleen			

Table 4. Individual Gross and Microscopic Observations – Males (Continued)

Animal ID: 13-0952			Group: 2
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Heart	No gross observed on tissue.		Hyperplasia, Mesothelium, Focal, Mild
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Minimal Infiltrate, mononuclear cell, Minimal
Lungs	Discoloration(s), Dark /Comments: red	Not Correlated	
Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:			
Kidneys; Spleen			

Table 4. Individual Gross and Microscopic Observations – Males (Continued)

Animal ID: 13-0967			Group: 2
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 4. Individual Gross and Microscopic Observations – Males (Continued)

Animal ID: 13-0968			Group: 2
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Mild

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 4. Individual Gross and Microscopic Observations – Males (Continued)

Animal ID: 13-0983			Group: 2
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Kidneys	No gross observed on tissue.		Nephropathy, Minimal
Liver	Discoloration(s), Mottled /Comments: mildly	Correlated	Infiltrate, mononuclear cell, Minimal Cytoplasm Vacuolization, Hepatocyte, Mild
Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:			
Heart; Spleen			

Table 4. Individual Gross and Microscopic Observations – Males (Continued)

Animal ID: 13-0984			Group: 2
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	Discoloration(s), Mottled /Comments: pale and mildly mottled	No Correlate	Infiltrate, mononuclear cell, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 5. Individual Gross and Microscopic Observations – Females

Animal ID: 13-1007			Group: 1
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Mild Infiltrate, mononuclear cell, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 5. Individual Gross and Microscopic Observations – Females (Continued)

Animal ID: 13-1008			Group: 1
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Mild Infiltrate, mononuclear cell, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 5. Individual Gross and Microscopic Observations – Females (Continued)

Animal ID: 13-1021			Group: 1
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Kidneys	No gross observed on tissue.		Cyst, Tubular, Minimal
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Minimal
Uterus	Hydrouterus	Not correlated	Not examined

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Spleen

Table 5. Individual Gross and Microscopic Observations – Females (Continued)

Animal ID: 13-1022			Group: 1
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Heart	No gross observed on tissue.		Cardiomyopathy, Minimal
Kidneys	No gross observed on tissue.		Hydronephrosis, Minimal Nephropathy, Minimal
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Minimal
Uterus	Mild Hydrouterus	Not correlated	Not examined
Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:			
Spleen			

Table 5. Individual Gross and Microscopic Observations – Females (Continued)

Animal ID: 13-1035			Group: 1
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Mild Infiltrate, mononuclear cell, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 5. Individual Gross and Microscopic Observations – Females (Continued)

Animal ID: 13-1036			Group: 1
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Minimal Infiltrate, mononuclear cell, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 5. Individual Gross and Microscopic Observations – Females (Continued)

Animal ID: 13-1005			Group: 2
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Kidneys	No gross observed on tissue.		Nephropathy, Minimal
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Minimal Infiltrate, mononuclear cell, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Spleen

Table 5. Individual Gross and Microscopic Observations – Females (Continued)

Animal ID: 13-1006			Group: 2
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Minimal Infiltrate, mononuclear cell, Minimal Necrosis, Hepatocyte, Focal, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 5. Individual Gross and Microscopic Observations – Females (Continued)

Animal ID: 13-1019			Group: 2
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Kidneys	No gross observed on tissue.		Nephropathy, Minimal
Liver			Cytoplasm Vacuolization, Hepatocyte, Minimal
			Infiltrate, mononuclear cell, Minimal
	Discoloration(s), Mottled /Comments: slightly	Not Correlated	
Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable: Heart; Spleen			

Table 5. Individual Gross and Microscopic Observations – Females (Continued)

Animal ID: 13-1020			Group: 2
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 5. Individual Gross and Microscopic Observations – Females (Continued)

Animal ID: 13-1033			Group: 2
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Kidneys; Spleen

Table 5. Individual Gross and Microscopic Observations – Females (Continued)

Animal ID: 13-1034			Group: 2
Day of Death: 14 (Core Necropsy)			
Tissue	Gross Observation(s)	Status	Microscopic Observation(s)
Kidneys	No gross observed on tissue.		Nephropathy, Minimal
Liver	No gross observed on tissue.		Cytoplasm Vacuolization, Hepatocyte, Mild Infiltrate, mononuclear cell, Minimal

Protocol tissues were examined grossly unless otherwise noted. All gross observations are listed above; tissues not listed were grossly unremarkable. The following tissues were examined microscopically and found unremarkable:

Heart; Spleen

ANIMAL USE PROTOCOL
U.S. ARMY PUBLIC HEALTH COMMAND
ABERDEEN PROVING GROUND. MD 21010-5403

PROTOCOL TITLE: Acute and Subacute Oral Toxicity of Periodate in Rats

PROTOCOL NUMBER: 30-13-06-01

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STUDY DIRECTOR/PRINCIPAL INVESTIGATOR (SD/PI):

Emily May Lent, Ph.D.
Toxicologist
Toxicity Evaluation Program
(410) 436-7749
emily.m.lent.civ@mail.mil

PRIMARY CO-INVESTIGATOR(S):

Lee C.B. Crouse (**Primary**)
Biologist
Toxicity Evaluation Program
(410) 436-5088
lee.crouse.civ@mail.mil

CO-INVESTIGATOR(S):

William Eck, Ph.D.
Biologist
Health Effects Research Program
(410) 436-7169
william.s.eck.civ@mail.mil

PROJECT SPONSOR:

Kimberly A. Watts
U.S. Army Research Development and Engineering Command (RDECOM)
Environmental Acquisition and Logistics Sustainment Program (AMSRD-FE)
3072 Aberdeen Blvd., Aberdeen Proving Ground, MD 21005

SPONSORS REPRESENTATIVE:

Mark Johnson, Ph.D., DABT
Director, Toxicology Portfolio
Army Institute of Public Health
5158 Blackhawk Road

Animal Use Protocol: Acute and Subacute Oral Toxicity of Periodate in Rats.

Aberdeen Proving Ground, MD 21010

ACRONYMS:

AIPH: Army Institute of Public Health
ALB: albumin
ALD: Approximate Lethal Dose
ALK P: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
ASTM: American Society for Testing and Materials
AMYL: amylase
ANCOVA: Analysis of Covariance
ANOVA: Analysis of Variance
AV: Attending Veterinarian
BRD: Biomedical Research Database
BUN: Blood Urea Nitrogen
CA: calcium
CAS: Chemical Abstracts Service
CFR: Code of Federal Regulations
CHOL: cholesterol
CO₂: carbon dioxide
CREA: creatinine
DOAC: DTIC Online Access Controlled
DOD: Department of Defense
EDTA: Ethylenediaminetetraacetic acid
ELISA: Enzyme-Linked Immunosorbent Assay
GLOB: globulin
GLP: Good Laboratory Practice
GLU: glucose
IACUC: Institutional Animal Care and Use Committee
IAW: in accordance with
KIO₃: Potassium Iodate
LD₅₀: median lethal dose
LS: Laboratory Sciences Portfolio, AIPH
NIS: Sodium/Iodide Symporter
PCOP: pentacalcium orthoperiodate
PHOS: inorganic phosphate
PI: Principal Investigator
QC: quality control
SD: Study Director
SOP: standing operating procedure
SSWP: Sequential Stage-wise Probit Method
T₃: triiodothyronine
T₄: thyroxine
TBIL: total bilirubin
TMB: 3,3',5,5'-Tetra-Methyl-Benzidine
TOX: Toxicology Portfolio

TSCA: Toxic Substance Control Act

TSH: thyroid stimulating hormone

TP: total protein

USAPHC: United States Army Public Health Command

USEPA: United States Environmental Protection Agency

I. NON-TECHNICAL SYNOPSIS:

Periodate salts, compounds rich in oxygen and iodine, are being developed as replacements for perchlorate as oxidizers in pyrotechnic formulations. Alternatives to perchlorate and other oxidizers are being pursued due to the health and environmental concerns associated with these compounds. The periodate salts have demonstrated good pyrotechnic performance and low moisture-sensitivity, making them good candidates. The health risks associated with these compounds have not, however, been determined. This study will assess the acute and repeated dose oral toxicity of periodate in rats. The acute toxicity of two periodate salts will be determined using the Sequential Stage-Wise Probit (SSWP) method in fasted rats, as well as the Approximate Lethal Dose method (ALD) in fed rats. A 14-day oral toxicity study will be performed in order to learn the effects of repeated daily dosing with a periodate salt. Rats will be dosed with either sodium periodate or potassium periodate via oral gavage and monitored throughout the study observation periods for body weight and clinical signs. At the conclusion of the exposure/observation period for each portion of the study, the rats will be anesthetized; blood samples will be collected from animals in the 14-day study, and a necropsy will be performed. Blood samples will be subjected to hematology, clinical chemistry and hormone analyses. Selected tissues will be weighed and processed for histopathology.

II. BACKGROUND

II.1. Background:

Existing toxicity data on periodate is limited to an intraperitoneal LD₅₀ in mice of 58 mg/kg for sodium periodate (Lewis, 1996) and an oral LD₅₀ of 7.07 g/kg for PCOP in fasted male rats (Kuhajek and Andelfinger, 1970). Oral exposure to PCOP caused central nervous system depression, gastrointestinal hemorrhage, hemolysis and renal congestion (Kuhajek and Andelfinger, 1970). Any number of these effects may have been attributable to iodate or iodide as metabolism studies have demonstrated that metaperiodate injected intravenously in rats is quickly reduced to iodate and subsequently to iodide (Taurog et al., 1966, Anghileri, 1965). Due to the rapid reduction of periodate to iodate and iodide, exposure of tissues to periodate in the present study may be minimal and may be limited to the gastrointestinal mucosa and liver. Exposure in many tissues may be primarily to iodate and iodide.

The toxicity of iodates and iodides varies greatly with the route of administration and the feeding state of the animal. Potassium iodate was 8.2 times more toxic than potassium iodide when given intraperitoneally to fasted mice; however, this difference was reduced to 1.8 times when given orally to fed mice (Webster et al., 1957). Sodium iodate and potassium iodate had nearly identical acute oral toxicity in mice, with LD₅₀ values of 505

mg/kg and 531 mg/kg, respectively, in fasted animals (Webster et al., 1957). Effects of sodium iodate and potassium iodate exposure included alternate hyperactivity and lassitude, weakness, prostration and dyspnea. Excitability, convulsions and paresis of the hind legs frequently preceded death. Transient increases in gastrointestinal pH and degeneration of parietal cells, hemolytic effects including hemoglobinuria and hemosiderin deposits in the kidneys, and non-specific fatty changes in the viscera were observed. Mortality was attributed to renal damage. Symptoms of sodium iodide and potassium iodide exposure were similar, except with slower onset and the absence of hemoglobinuria (Webster et al., 1957). Iodate salts have also been demonstrated to produce toxic retinopathy in animals and humans at doses of 40 mg/kg (IV) in rats and 187 mg/kg (oral) in humans (Singalavanija et al., 2000).

Data from repeated dose studies are limited. In an 8-week feeding study in rats, mortality was observed at 20,000 ppm PCOP. These animals also exhibited reduced hemoglobin and hematocrit values, severe body weight depression, lethargy and muscle weakness, pale/small spleens, and distended intestines containing pink mucous. Thyroid weight was increased in females in the 2,000 ppm PCOP group; thyroid weight was not evaluated in the 20,000 ppm group (Kuhajek and Andelfinger, 1970). In a 16-week study in which potassium iodate was administered to mice via drinking water, hemolysis and associated renal damage were observed at doses of 0.25% KIO₃ (approximately 540 mg/kg-day) and above (up to 1231 mg/kg-day), but no other adverse effects were observed. In a similar four-week study with guinea pigs, no effects were observed at doses up to 0.50% KIO₃ (approximately 485 mg/kg-day; LD₅₀ in guinea pigs <400 mg/kg-day) (Webster et al., 1959). The authors concluded that these results demonstrated that the toxicity of iodate is reduced when consumed in divided doses over time, when given with food (Webster et al., 1959). The lowered toxicity may be attributable to small doses of iodate being reduced to the less toxic iodide when in contact with food in the gastrointestinal tract.

The toxicity of periodate to the thyroid is of particular importance. Iodine is essential for normal thyroid function. Iodide is taken up by thyroid follicular cells, transported into the lumen, oxidized to iodine and used to make thyroid hormones (T₃ and T₄). Alteration of blood iodine levels can have profound effects on thyroid status. Dietary supplementation with iodized salt has long been practiced as a preventative measure and treatment for iodine-deficient goiter. Excess dietary iodide can also result in thyroid hyperplasia and goiter. High blood iodide levels disrupt thyroxinogenesis by blocking the release of T₃ and T₄ from the follicle (Capen and Martin, 1989). Iodate and iodide have been shown to be equally available to the thyroids of rats, rabbits, and humans (Burgi et al., 2001, Murray, 1953). Therefore, the increase in available iodine with periodate dosing may result in iodine-induced thyrotoxicosis.

To determine whether sodium periodate and/or potassium periodate provide reduced health hazard alternatives to currently fielded oxidizers, acute and subacute toxicity tests will be conducted in rats.

II.2. Literature Search for Duplication:

Animal Use Protocol: Acute and Subacute Oral Toxicity of Periodate in Rats.

II.2.1. Literature Source(s) Searched: BRD, DOAC Technical Reports, DOAC Research in Progress, FEDRIP, PubMed, Web of Science

II.2.2. Date of Search: 21 May 2013

II.2.3. Period of Search: 1900 - 2013

II.2.4. Key Words of Search: (metaperiodate or periodate or sodium periodate or potassium periodate or iodate*) and (toxic or toxicity) and ((sequential stage-wise or sequential stage wise or sequential stagewise) and (probit)) and (rat or rats)

II.2.5. Results of Search: A total of 105 references resulted from the literature search that was performed using the key words listed above in all the listed databases. However, no studies for sodium periodate or potassium periodate acute or subacute toxicity were found that would suggest that this study would be a duplicate effort. As such, the present study is not a duplication of the information available in the literature.

III. OBJECTIVE/HYPOTHESIS:

The objectives of this study are to determine the oral LD₅₀, 95% confidence intervals and slope of the curve for sodium periodate and potassium periodate in the rat and to determine the effects of repetitive oral exposure to either sodium periodate or potassium periodate in male and female rats.

IV. MILITARY RELEVANCE:

Periodates, anions composed of iodine and oxygen, are being developed as alternatives to perchlorates and barium nitrate for use as an oxidizer in military incendiary devices (Fields, 2012, Ball, 2012, Moretti et al., 2012). Alternatives to perchlorate and barium nitrate are being pursued due to the environmental and health hazards associated with these compounds. The use of perchlorate has been widely scrutinized due to the potential for the compound to cause thyroid dysfunction and developmental abnormalities. Health effects associated with barium nitrate include cardiac and respiratory failure. Sodium and potassium periodate have been identified as potential replacement incendiary oxidizers that fulfill the pyrotechnic requirements and are presumed, based on structure, to be less toxic than those currently in use. Periodate ions are larger than perchlorate ions, leading munitions developers to speculate that perhaps the ions are too big to interact with thyroid receptors in the same manner as perchlorate (Ball, 2012, Fields, 2012, Moretti et al., 2012). If passed by the NIS, however, the ions will bring atomic iodine into the follicular lumen of the thyroid that will then be convertible to thyroid hormones. These theories are not currently supported by experimental data as the toxicity of periodate has not been investigated.

V. MATERIALS AND METHODS

Test Article: This study will be conducted with sodium periodate and potassium periodate. If a certificate of analysis is not provided by the manufacturer, a neat sample of the test articles will be submitted to LS for purity determination. The periodate(s) will be mixed with deionized water. Stability of the test article in water will be determined

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prior to conduct of the subacute study. Samples of all dosing solutions will be submitted to LS for concentration verification. Neat test material will be stored in anti-static bags or sample jars in a separate storage cabinet for oxidizers, away from reducing agents. Sample analysis will be done IAW SOP DLS 801.1 (USAPHC, 2012).

Test Substance Chemical/Physical Properties

Name	Sodium periodate	Potassium periodate
Synonym	Periodic acid sodium salt	Periodic acid potassium salt
CAS#	7790-28-5	7790-21-8
Physical State	Colorless tetragonal crystals	Colorless powdered solid
Molecular Formula	NaIO ₄	KIO ₄
Molecular Weight	213.91	230.01
Density	3.87 g/cm ³	3.618 g/cm ³
Solubility	Soluble in cold water (144g/L @25°C), sulfuric, nitric, acetic acids	Very slightly soluble in cold water (4.2g/L @20°C; 6.5g/L @30°C)

V.1. Experimental Design and General Procedures:

The acute and subacute oral toxicity of sodium and potassium periodate, pyrotechnic oxidizers, will be determined using a series of laboratory studies in rats. The acute toxicity in fasted rats will first be conducted using the SSWP method to determine the LD₅₀ for both sodium and potassium periodate. An ALD will also be conducted using either sodium or potassium periodate in fed rats to determine if differences exist between fasted and fed lethal doses and to assist in setting dose levels in the subacute study. Based upon the results of the SSWP, a 14-day oral toxicity study will be performed to determine the effects of repeated daily dosing with either sodium or potassium periodate.

Group	No. of Male Rats	No. of Female Rats	Pain Category
SSWP			
Sodium periodate	30	30	40C / 20E
Potassium periodate	30	30	40C / 20E
	TOTAL = 60	TOTAL = 60	TOTAL = 80C / 40E
ALD			
Periodate		7	4C / 3E
		TOTAL = 7	TOTAL = 4C / 3E
Subacute Study			
Vehicle Control	10	10	20D

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Periodate Dose 1	10	10	20D
Periodate Dose 2	10	10	20D
Periodate Dose 3	10	10	20D
Periodate Dose 4	10	10	20D
Periodate Dose 5	10	10	10D/10E
	TOTAL = 60	TOTAL = 60	TOTAL = 110D / 10E
	GRAND TOTAL = 120	GRAND TOTAL = 127	GRAND TOTAL = 84C / 110D / 53E

V.1.1. Acute Study:

The acute toxicity of sodium periodate and potassium periodate will be assessed using the SSWP method (Feder et al., 1991a, Feder et al., 1991b, ASTM, 2010). This method proceeds in stages in which groups of rats are dosed and the responses observed and used in determining the doses and animal numbers used in the next stage of dosing. In the first stage, approximately five different doses of the test compound will be selected such that the doses span the entire dose response curve. In the absence of historical data or literature values, doses for the first stage of dosing may be set at the default starting value of 175 mg/kg with half-log dose intervals (3.2 dose progression factor) (USEPA, 2002). One to two animals will be given each dose in the first stage of the study. In all subsequent stages of dosing, one to four doses will be used, with one to three animals at each dose. Animals will be randomly assigned to doses. Dosing of stages is separated by a post-dosing observation period of up to 14-days in which animals are observed for signs of toxicity, moribundity and mortality. This period may be reduced (i.e., to 24-48 hours) for determination of dosages in subsequent stages if confident in the survival of the animals. A probit analysis of the results from all previous stages of dosing will be used to determine the doses for subsequent stages of dosing. The analysis uses the results from each stage to calculate the LD₅₀, 95% confidence interval, and slope of the dose response curve. Dosing of stages will be continued until the variation around the LD₅₀ is less than 0.40 (95% upper confidence limit minus 95% lower confidence limit/2x the LD₅₀) or a maximum of 30 rats per sex have been utilized. If no deaths are observed at the highest dose level (2000 mg/kg) in the first stage of dosing, a limit test will be conducted. In the limit test, five additional animals will be dosed at 2000 mg/kg. Three or more animals must survive the limit test for the LD₅₀ to be determined to be greater than the limit dose.

An ALD will also be conducted on the periodate salt to be tested in the subacute study. The periodate salt to be tested in the ALD and subacute studies will be the more toxic of the two periodate salts, based on preliminary results of the SSWP. If no substantial difference exists in the acute toxicity, the periodate salt for further study will be selected based on water solubility and consideration of the toxicity of the sodium and potassium levels to be used (i.e., if potassium toxicity will impact the study results, sodium periodate will be selected). This test will be conducted in fed rats to assist in determining the dose levels for the subacute study. This phase of the study will be conducted in a single sex to determine a dose adjustment factor between fasted (overnight) and fed rats. Six female rats will be given periodate via oral gavage, with

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one rat receiving each dose. One additional rat will be dosed with the vehicle (distilled water). Dose intervals will be set at approximately 1.5x the previous dose up to a maximum of 2000 mg/kg. The starting dose will be based on the results of at least the first stage of the SSWP and the approximately 2-fold difference between LD_{50s} in fasted and fed rats for iodate. All animals will be dosed on the same day and observed for a period of up to 14 days thereafter for mortality and signs of toxicity. All animals will be submitted for gross necropsy. The ALD will be defined as the lowest dose which is lethal where two successively higher doses are lethal and three lower doses are not lethal.

V.1.1.1. Test Substance Preparation and Administration:

The test substance will be dissolved or suspended in distilled water. Dosing solutions will be prepared shortly before dosing unless stability analyses have been completed. Constant concentration dosing via oral gavage will be used unless deemed impractical based on maximum dose volume restrictions and minimum feasible delivery volumes. The maximum dose volume given in a single dose will not exceed 10 mL/kg of body weight; however, multiple divided doses may be given over a period of time not exceeding 24 hours. For the SSWP, animals will be fasted overnight prior to dosing and for 3-4 hours following test substance administration. Doses will be calculated according to the body weight measured on the day of dosing.

V.1.1.2. Observations

A thorough physical examination of each rat will be performed by study personnel at a similar time at least once per day during the 14-day observation period. The examination process will consist of each rat being removed from its home cage, individually handled, and carefully observed. Observations will include, but not be limited to, evaluation of skin and fur, eyes and mucous membranes, respiratory and circulatory effects, autonomic effects such as salivation, central nervous system effects, including tremors and convulsions, changes in the level of activity, gait and posture, reactivity to handling or sensory stimuli, altered strength, and stereotypes or abnormal behavior (e.g., self mutilation, walking backwards). All data related to the observation of rats will be detailed and thoroughly documented in the study records by study personnel.

V.1.1.3. Body Weight and Food Consumption:

Animals will be weighed prior to test substance administration, at least weekly thereafter, and at termination. Food consumption will be monitored at least weekly by weighing the food hopper.

V.1.1.4. Gross Necropsy, Tissue Collection and Preservation:

At the time of termination, animals will be euthanized as described in section V.4.6. Animals will then be necropsied and examined macroscopically for any structural abnormalities or pathological changes. Tissues may be removed, weighed and processed as described in sections V.1.2.4.2 and V.1.2.4.3, at the discretion of the PI/SD.

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V.1.2. Subacute Study:

The subacute study will have 5 dose groups, along with a vehicle control group, consisting of 10 males and 10 females for each dose group [$N=(10+10) \times 6=120$]. Stratified random assignment of animals to dose groups will be used, with animals stratified by weight. Animals will be dosed daily via oral gavage (as described in section V.4.4.8.1.) with either sodium or potassium periodate in distilled water for 14-days (7 days per week). The periodate salt used will be determined as described in section V.1.1. Dose selection will be based on the results of the SSWP (e.g., 1x, 0.75x, 0.5x, 0.25x, 0.125x, 0.0625x, 0.03125x the LD_{50}) with an adjustment factor, if needed, for differences in fed and fasted rats based on the results of the ALD. The vehicle control group will receive a volume equivalent to the highest exposure group. All rats will be monitored throughout the study for body weight changes and clinical signs of toxicity. Fasted blood samples will be collected at termination and subjected to clinical chemistry, hormone and hematology assessments (as described in section V.4.4.3.1.).

V.1.2.1. Test Substance Preparation and Administration:

The test substance will be dissolved or suspended in distilled water. Constant volume dosing via oral gavage will be used. The maximum dose volume given in a single dose will not exceed 10 mL/kg of body weight; however, multiple divided doses may be given over a period of time not exceeding 24 hours. Doses will be calculated according to the most recent body weight. Initiation of administration of periodate may be staggered by 2-5 days to facilitate necropsy. An approximately equal number of animals per dose group will be placed in each starting group.

V.1.2.2. Observations:

A thorough physical examination of each rat will be performed by study personnel at a similar time at least once per day. The examination process will consist of each rat being removed from its home cage, individually handled, and carefully observed. Observations will include, but not be limited to, evaluation of skin and fur, eyes and mucous membranes, respiratory and circulatory effects, autonomic effects such as salivation, central nervous system effects, including tremors and convulsions, changes in the level of activity, gait and posture, reactivity to handling or sensory stimuli, altered strength, and stereotypes or abnormal behavior (e.g., self mutilation, walking backwards). All data related to the observation of rats will be detailed and thoroughly documented in the study records by study personnel.

V.1.2.3. Body Weight and Food Consumption:

Animals will be weighed on days -3, -1, 0, 1, 3, 7, and 14. Food consumption will be monitored by weighing the food hopper on days 0, 1, 3, 7, and 14.

V.1.2.4. Terminal Observations

V.1.2.4.1. Clinical Chemistry, Hematology and Hormone Assays:

Fasted blood samples will be taken from all animals at termination (as described in section V.4.4.3.1.) and subjected to hematology, clinical chemistry and hormone analyses. The following hematology parameters will be evaluated: hematocrit, hemoglobin concentration, erythrocyte count, total and differential leukocyte count, platelet count, and clotting time. Serum will be evaluated for the following chemistries and hormones: BUN, CREA, GLU, TP, ALB, ALT, ALK P, AMYL, AST, GLOB, CHOL, TBIL, CA, PHOS, electrolytes, T₃, T₄, and TSH. Details concerning clinical chemistry and hematology analyses are outlined in TOX SOP 011 and TOX SOP 013, respectively (USAPHC, 2013a, USAPHC, 2013b).

V.1.2.4.2. Gross Necropsy, Organ Weight and Tissue Preservation:

At the time of termination or premature death, all animals will be necropsied and examined macroscopically for any structural abnormalities or pathological changes. Wet weights of the organs listed below from all animals will be determined as soon as possible after dissection to avoid drying. Testes and epididymides from each animal will be placed in Davidson's fixative overnight (no longer than 24 hours) or 10% buffered formalin for at least 24 hours; however, fixing in Davidson's solution for less than 24 hours is preferred. The fixative used will be documented in the study records. All other organs will be placed in 10% buffered formalin for at least 24 hours for fixation. All gross pathology changes will be recorded on CHPPM form 333. This tissue list may be altered at the discretion of the study staff based on observed toxicity and gross pathology findings.

- Uterus (with oviducts and cervix)
- Ovaries
- Testes
- Epididymides
- Brain
- Liver
- Kidneys
- Heart
- Spleen
- Thymus
- Thyroid (weighed after fixation)
- Adrenal glands

In addition to the organs listed above, samples of peripheral nerve, muscle, spinal cord, eye plus optic nerve, gastrointestinal tract, urinary bladder, lung, trachea (with thyroid and parathyroid attached), bone marrow, pituitary, and vagina will be collected and will be placed in 10% buffered formalin for at least 24 hours for fixation. All training of necropsy personnel will be verified prior to any necropsy procedures. Personnel and the procedures they perform will be documented at the time of necropsy.

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V.1.2.4.3. Histopathology:

Full histopathology of the organs listed in section V.1.2.4.2. will be performed for all high-dose and control animals. Organs demonstrating treatment-related changes may also be examined in animals in the lower dose groups. Additionally, all gross lesions will be subjected to histopathological evaluation.

V.1.3. Study Time Frame:

Estimated initiation date for the study is July 2013. Estimated completion date for the study is October 2013.

V.2. Sample Size Evaluation, Data Analysis Plan, and Archiving of Data:

Sample sizes were selected in accordance with the EPA Health Effects Testing Guidelines (USEPA, 2000, USEPA, 2002). These sample sizes have been widely used and have been demonstrated to provide adequate statistical power in these methods.

Data from the SSWP will be analyzed according to the methods of Feder et al. (Feder et al., 1991a, Feder et al., 1991b) to determine the LD₅₀, 95% confidence interval, and slope of the dose response curve. The ALD, as determined in section V.1.1., will be compared to the LD₅₀ from the SSWP to estimate, if necessary, an adjustment factor between fasted and fed rats for use in determining doses for the subacute study. For variables that are measured only at the end of the study, the dose groups will be compared using a one-factor ANOVA. Organ to brain and organ to body weight ratios will be calculated and analyzed similarly to the other parameters measured at the end of the study. If the dose group effect is significant, post hoc tests will be used to compare pairs of dose groups and dose groups to the control group; a Tukey's multiple comparison test if the variance of the groups is similar and a Dunnett's T3 test if the variances are unequal. Data will be tested for normality and log transformed and retested if significantly different from normal. Variance equality will be determined by a Levene's test.

For absolute organ weights, comparison of the dose groups will be made using an ANCOVA, with body weight at the end of the study being the covariate used. Even though the dose groups will be assigned at Day 0 to keep the average weight for each dose group similar, the weights can change during the study dependent on the dose group. The ANCOVA will adjust for any differences in body weights among the dose groups at the end of the study, because heavier animals would tend to have heavier organs. If the dose group effect is significant, an appropriate post hoc test will be used to compare pairs of dose groups and dose groups to the control group.

Dose groups will also be compared with respect to absolute body weights, as well as weekly changes in body weight and net weight changes using a repeated measures ANOVA. Dose groups will also be compared with respect to net food consumption for the study using a one-factor ANOVA. If the ANOVA is significant, the post hoc tests will be used to compare pairs of dose groups; a Tukey's multiple comparison test if the

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variance of the groups are similar, and a Dunnett's T3 test if the variance are unequal. Variance equality will be determined by a Levene's test.

Other observational data including gross necropsy observations and histopathology data may be converted to categorical data and analyzed using a Chi-square or Fisher's exact test.

An appropriate statistical software package, such as SPSS[®] and/or SAS[®] will be used to perform all analyses and statistical significance will be defined as $p \leq 0.05$ for all tests.

This study will be conducted in a manner consistent with the principles of 40 CFR Part 792 TSCA GLP Regulation (CFR, 1989). The investigators and technicians will adhere to the Guide for Care and Use of Laboratory Animals (NRC, 2011).

Records will be kept in standard USAPHC laboratory notebooks and/or three ring binders. Daily records will be kept on survival and clinical signs collected on the animals during the study. Procedures for preparation of any euthanasia solution, drug administration, animal blood collection, observation logs, morbidity/mortality logs, etc., will be stored with the study records. All post mortem procedures not listed in this protocol will be documented in the study records and kept with the study raw data. These records will be made available to oversight organizations such as the USEPA, Quality Systems Office, and the IACUC. The protocol, protocol amendments, raw data, statistical analysis, tabular calculations, and graphic analysis of the data will be saved with the study records. Additionally, memoranda to the study file, study logs, signature logs, final reports, and final report amendments will be archived at USAPHC. Some ancillary records such as maintenance and calibration logs, environmental monitoring logs, animal room husbandry and health rounds sheets, training files, etc. may be stored in the archives but not stored with the study files.

V.3. Laboratory Animals Required and Justification

V.3.1. Non-animal Alternatives Considered:

The objectives of this study are to determine the LD₅₀ and subacute toxicity of periodate. There are no appropriate animal substitutes (e.g., computer models, tissue/cell cultures) that simulate the pharmacokinetics and pharmacodynamics of *in vivo* animal exposure. No non-animal alternative would provide the necessary toxicological information provided by this study. Therefore, it is necessary to perform this study in an animal model.

V.3.2. Animal Model and Species Justification:

Sprague-Dawley is the strain of rat that has been historically used for oral toxicity studies by USAPHC TOX and is the recommended species due to an historical and extensive database.

V.3.3. Laboratory Animals

V.3.3.1. Genus species: *Rattus norvegicus*.

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V.3.3.2. Strain / Stock / Breed: Sprague-Dawley (CrI:CD(SD))

V.3.3.3. Source / Vendor: Charles River Laboratories, Wilmington, MA (USDA 14-R-0144)

V.3.3.4. Age: Acute Study: 7-9 weeks old on arrival

14-Day Study: 6-8 weeks old on arrival

V.3.3.5. Weight: Appropriate for age

V.3.3.6. Sex: Male and female (nulliparous and non-pregnant)

V.3.3.7. Special Considerations: None

V.3.4. Number of Animals Required (by Species): 247

V.3.5. Refinement, Reduction, Replacement (3 Rs):

V.3.5.1. Refinement:

Standard rat enrichment will be implemented in accordance with TOX SOP 033(USAPHC, 2013h). Animals will be socially housed on this study. All animals on this study will be handled on a frequent basis and provided a form of environmental enrichment (e.g., nylabones, rodent retreats) throughout the study period. Animals will be considered for early removal from this study as described in section V.4.5. Animals will be anesthetized prior to painful procedures as described in section V.4.1.2.1.

V.3.5.2. Reduction:

The SSWP method uses fewer animals than other traditional methods of LD₅₀ determination and provides quantitative estimates of the LD₅₀, slope and confidence intervals. If the limit dose (2000 mg/kg) does not cause mortality in the first stage of the SSWP, then the second stage will revert to the limit test and use a maximum of 5 males and 5 females to estimate the LD₅₀. The 14-day study will be conducted on only one salt of periodate, reducing animal use. In addition, limiting the duration of the subacute study to 14-days rather than the typical 28-days may reduce the pain and distress experienced in some dose groups.

V.3.5.3. Replacement:

No non-animal alternatives are known to exist that will provide the required data. At this time, there are no non-animal alternatives that can fully replicate the complex processes that occur within an intact mammalian organism.

V.4. Technical Methods:

V.4.1. Pain / Distress Assessment:

V.4.1.1. APHIS Form 7023 Information:

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V.4.1.1.1. Number of Animals

V.4.1.1.1.1. Column B: 0

V.4.1.1.1.2. Column C: 84

V.4.1.1.1.3. Column D: 110

V.4.1.1.1.4. Column E: 53

V.4.1.2. Pain Relief / Prevention

V.4.1.2.1. Anesthesia / Analgesia / Tranquilization:

Animals will be anesthetized with CO₂ prior to blood collection. Animals will be brought to the necropsy room in their home cage or in a transport cage. A stainless steel lid will be placed on the cage. If using a transport cage, the grommet will be covered with tape or a magnet. The CO₂ tank will be turned on, then the regulator opened to approximately ½ turn, and the flowmeter set to 5 L/minute. Animals will remain in the cage until they are recumbent, but breathing regularly. Once recumbent, a toe or space between the toes will be pinched to assess appropriate depth of anesthesia. If no response to the toe pinch, animals will be removed and blood collected (as described in V.4.4.3.1.). Upon completion of blood collection animals will be returned to the cage and euthanized IAW TOX SOP 027 (USAPHC, 2013g).

V.4.1.2.2. Pre- and Post-procedural Provisions:

A physical examination will be made at least once each day during all phases of the study. Observations will be detailed and carefully recorded in the study records. Details related to observations and/or physical examination of rats are described in Sections V.1.1.2. and V.1.2.2.

V.4.1.2.3. Paralytics: N/A

V.4.1.3. Literature Search for Alternatives to Painful or Distressful Procedures:

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V.4.1.3.1. Source(s) Searched: FEDRIP, PubMed, Web of Science

V.4.1.3.2. Date of Search: 21 May 2013

V.4.1.3.3. Period of Search: 1900 - 2013

V.4.1.3.4. Key Words of Search: (metaperiodate or periodate or sodium periodate or potassium periodate or iodate*) and (toxic or toxicity) and ((sequential stage-wise or sequential stage wise or sequential stagewise) and (probit)) and ((cardiac blood collect*) or (heart and blood and collect*) or (median lethal dose or mld or lethal dose 50 or ld 50 or ld50 or ld-50)) and (pain or distress or * or refin* or reduc* or replac* or artificial or vitro or culture or tissue or cell or organ or insect or arachnid or invertebrate or fish or mollusc or cephalopod or simulat* or digital or interactive or mannequin or manikin or model)

V.4.1.3.5. Results of Search: The literature search identified 2 references pertaining to alternatives to painful procedures. However, no acceptable alternatives to the painful or distressful procedures (e.g., LD₅₀, cardiac bleed) in this protocol were found. Although other methods exist for blood collection (e.g., saphenous vein, dorsal pedal vein, tail vein) from the laboratory rat, none of these alternative methods would allow collection of a sufficient volume of blood to perform clinical chemistry, hematology, and hormone analyses.

V.4.1.4. Unalleviated Painful or Distressful Procedure Justification:

The nature of these studies precludes the use of totally painless procedures. An attempt to alleviate pain or distress by the administration of anesthetics, analgesics, or drugs may alter the manifestation of the toxic responses. Typical pain relievers such as opiates and non-steroidal anti-inflammatories as well as anesthetics have the ability to mask certain toxic signs that may be observed due to the administration of the test compound, especially those signs resulting from pain or distress. In addition, certain side effects such as alterations in blood chemistry and hematology may arise from the use of these drugs and could be misinterpreted by the investigator as clinical signs caused by the test material. The observation of the onset, duration and/or reversibility of toxic signs is critical to mechanistic interpretation, especially since the acute study is being used to set dosages for a longer-term study. "Toxic signs" are defined in TOX SOP 026 (USAPHC, 2013f). Animals determined to be moribund with no possibility for recovery will be euthanized as described in section V.4.6. However, unalleviated pain and mortality is expected to occur in the determination of a median lethal dose.

V.4.2. Prolonged Restraint and Restraint Methods: N/A

V.4.3. Surgery

V.4.3.1. Pre-surgical Provisions: N/A

V.4.3.2. Procedure: N/A

V.4.3.3. Post-surgical Provisions: N/A

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V.4.3.4. Location: N/A

V.4.3.5. Surgeon: N/A

V.4.3.6. Multiple Survival Operative Procedures

V.4.3.6.1. Procedures: N/A

V.4.3.6.2. Scientific Justification: N/A

V.4.4. Animal Manipulations

V.4.4.1. Injections: None

V.4.4.2. Use of Non-pharmaceutical-grade chemicals:

The compounds being tested are not available in a pharmaceutical-grade composition. They are under investigation as described in the objective section (III) of this protocol.

V.4.4.3. Biosamples:

V.4.4.3.1. Blood Collection and Analysis:

Blood will be collected from all animals at termination of the 14-day study. All blood collection will be conducted under CO₂ gas anesthesia (as described in section V.4.1.2.1) just prior to euthanasia. Once the anesthetic has taken effect (ensured by a toe pinch), the rat will be placed in dorsal recumbency. The rat can then be immobilized by either holding the base of the tail or by holding the forelimbs apart and upward with the thumb and index finger. There should be no response by the rat to entry of the needle into its skin. If there is any response, the rat is not at a deep enough level of anesthesia for this method of blood collection and the procedure will stop until the rat is anesthetized to a deeper plane of anesthesia. An appropriate size needle (18-25 gauge, 1-1.5 inch needle, depending on the size of the rat) will be fitted onto a 1-6 mL syringe and inserted anteriorly under the xiphoid region of the rat at an approximately 45° angle and advanced firmly through the diaphragm and into the heart. Slight negative pressure will be placed on the syringe plunger and the required amount of blood withdrawn from the rat. The goal of the blood draw is to obtain as large a sample as possible, and is generally 3-6 mL. Following collection of the blood sample, the needle will be slowly withdrawn from the rat. To minimize blood hemolysis, the needle should be removed from the syringe before discharging the blood sample into microtubes. Blood collection will be promptly followed by euthanasia as described in section V.4.6.

For hematology samples, approximately 1-2 mL of blood will be transferred to an EDTA microtube and immediately inverted gently several times. For clinical chemistry and hormone samples, approximately 1-2 mL of blood will be transferred to a serum-gel microtube and allowed to stand at room temperature for at least 20 minutes to allow sufficient clotting prior to centrifugation. The remainder of the blood from each animal (approx. 1-2 mL) will be transferred to a sodium citrate microtube for analysis of prothrombin time. Details concerning clinical chemistry and hematology parameters are

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outlined in TOX SOP 011 and TOX SOP 013, respectively (USAPHC, 2013a, USAPHC, 2013b). For hormone analyses, serum will be removed and assayed immediately or aliquotted into microcentrifuge tubes and stored at -20 °C or colder for subsequent analyses. Hormonal measurements will be conducted using ELISA and/or time-resolved immunofluorescent procedures. Details concerning use of the TOSOH® Automated Enzyme Immunoassay System for measurement of thyroid and reproductive hormones are outlined in TOX SOP 020 (USAPHC, 2013c).

Analysis of TSH will be conducted using a rat TSH ELISA kit per the manufacturer's (ALPCO Immunoassays or similar) instructions (ALPCO, 2012). Briefly, 25 µL of a standard, blank, or sample will be added to the appropriate wells, 200 µL of enzyme-labeled anti-rat TSH-antibody added to all wells, the plate covered with the adhesive strip, and incubated for 18-20 hours at 4±2°C. Liquid will then be aspirated from each well and the plate washed 4 times (Wash: Each well filled with diluted wash solution (300 µL) and let stand for 2 minutes, then liquid removed by flicking the plate over a sink. The remaining drops are removed by patting the plate on a paper towel). The TMB Substrate Solution (200 µL) will be added to each well and the plate incubated in the dark for 10-30 minutes (timing based on color development), keeping the plate away from drafts and other temperature fluctuations. Stop Solution (50 µL) will be added to each well when the first four wells containing the highest concentration of standards develop obvious blue color. The optical density of each well will be determined within 30 minutes, using a microplate reader set to 450 nm. Test samples and QC samples will be run in duplicate, with QC samples dispersed among the test samples.

V.4.4.4. Adjuvants: N/A

V.4.4.5. Monoclonal Antibody (MAb) Production: N/A

V.4.4.6. Animal Identification:

Animals will be identified by cage cards according to TOX SOP 024 (USAPHC, 2013e). An identification number (e.g., the last 3 digits of the animal number) will also be marked on the tail of each rat with a water-insoluble marker in order to ensure proper identification of rats when removed from their cages or when group-housed.

V.4.4.7. Behavioral Studies: N/A

V.4.4.8. Other Procedures:

V.4.4.8.1. Oral Gavage:

Each rat will be gently restrained by placing the index and middle finger on either side of the animal's neck with the remainder of the hand used to support the body. Just prior to dosing, the index and middle finger can be used to tilt the animal's head back and the gavage needle inserted into either the side or the top of the mouth. The rat may also be "scruffed" by pinching the skin at the base of the neck, behind the ears, between the thumb and fingers. The gavage needle is then gently slid down the animal's esophagus until the hub of the gavage needle is at the opening of the animal's mouth. The 16 gauge x 2-3 inch gavage needle is the correct length to allow for the proper placement

of the test material in young adult rats. If any resistance is felt during the gavage procedure, the gavage needle is removed and the animal is briefly released before the procedure is attempted again. Once the material has been dispensed, the animal is briefly observed for any signs of aspiration.

V.4.4.9. Tissue Sharing: Tissues from animals euthanized on this study may be made available to other personnel with approved protocols if coordinated through the PI/SD and the AV. Tissue sharing will be allowed only if doing so does not affect the quality and validity of the study or change the euthanasia methods.

V.4.5. Study Endpoint:

The study endpoint of the Acute Study is intervention euthanasia of moribund animals, study-related mortality or euthanasia following an observation period not to exceed 14-days. The study endpoint of the Subacute Study is intervention euthanasia of moribund animals and euthanasia on the day following the final administration of the test substance.

Although some form of euthanasia is the projected study endpoint, the possibility still exists that a compound-related death may occur during an unobserved period (i.e., overnight). The novelty of the compound being tested prevents the assurance that a compound-related death may not occur. Additionally, the time at which signs of toxicity appear, their duration, and the time to death are important, especially if there is a tendency for deaths or morbidity to be delayed or if the signs of toxicity are reversible or recovery is possible. This is particularly important in the acute study when the type, onset and duration of toxic signs are still unknown. As such, potentially moribund animals will be monitored, in consultation with the AV, during the acute study for possible reversal and recovery of toxic signs.

Animals will be assessed for moribundity based on a weight of evidence of the following signs: impaired ambulation which prevents animals from reaching food/water; excessive weight loss or emaciation ($\geq 20\%$ body weight loss compared to controls); lack of physical or mental alertness; prolonged labored breathing (e.g., lasting longer than 8 hours and accompanied by extreme lethargy); unabated seizure activity (e.g., lasting longer than 1 hour); inability to urinate or defecate for greater than 24 hours; or a prolonged inability to remain upright (e.g., lasting more than 2 hours). The AV may be consulted, if needed, to evaluate potentially moribund animals, unless the PI/SD plans to immediately euthanize the animal. Intervention euthanasia will be conducted on animals determined to be moribund.

Any animals not used in the SSWP method will either be transferred to another approved protocol or euthanized as described in section V.4.6.

V.4.6. Euthanasia:

Euthanasia will be accomplished by asphyxiation from CO₂ exposure IAW TOX SOP 027 (USAPHC, 2013g). Death of all rats euthanized by CO₂ will be ensured by thoracotomy or immediate necropsy with perforation of the diaphragm. Thoracotomy will be accomplished by inserting a sharp blade into the chest cavity behind a rib and

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moving the blade the length of the rib. Alternatively, for animals being immediately necropsied, the abdomen will be opened and a puncture made through the diaphragm via the abdominal cavity.

V.5. Husbandry & Veterinary Care:

V.5.1. Husbandry Considerations:

Animal rooms will be maintained IAW TOX SOP 022 (USAPHC, 2013d). Animals will be provided ad lib rodent chow that is certified free of contaminants (with exception of overnight fasting prior to dosing for the Acute Study and prior to necropsy). Water will be provided ad lib by the automated watering system, by reservoirs that feed into the racks, or by water bottles. Light cycle will be 12 hours on and 12 hours off. Room temperature will be set at 68-72°F and humidity at 30-70%. Cage sanitation will be checked at least once daily by animal care staff. The animals will be housed in plastic, solid-bottom shoebox cages (size appropriate to the body weight of the rat). Rats will be same-sex group housed within treatment group during the Subacute Study. The Acute Study animals will be singly housed following dosing due to the unknown toxicity of the compound. Animals showing no signs of toxicity during the first 7±2 days of the observation period may be pair housed again at the discretion of the PI/SD and AV. Pair housed animals showing signs of delayed toxicity will be returned to single housing. All rats will undergo a 5-day acclimation period. Body weight and observation data may also be collected for rats by study personnel during the acclimation period in an attempt to more accurately monitor the health status of the rats in preparation for their use on study. However, animals will not be weighed or handled by study personnel within the first 24 hours after their arrival to the facility.

V.5.1.1. Study Room:

Studies will be conducted at the AIPH TOX animal facility, Bldg E-2100 or Bldg E-2101, housing room as assigned. All live animal work will occur in the housing room.

V.5.1.2. Special Husbandry Provisions:

Food consumption for all study animals will be monitored based on the weight of the food hopper. Therefore, feed should not be added to feeders and feeders should not be replaced without consulting the PI/SD. Food enrichment may not be used due to food consumption monitoring. When animals are being fasted, PI/SD or study staff (or Vet Med staff when directed to do so) will remove the food hopper no later than 1800 and no earlier than 1200 the day prior to dosing or necropsy. Animals on the Acute Study will be dosed after 12-18 hours of fasting. The feeder will be returned 3-4 hours following dosing. Fasting of rats will not exceed 24 hours before necropsy or during the Acute Study dosing.

V.5.1.3. Exceptions:

The Acute Study animals will be singly housed after dosing. Animals showing no signs of toxicity during the first 7±2 days of the observation period may be pair housed again at the discretion of the PI/SD and AV. Pair housed animals showing signs of delayed

toxicity will be returned to single housing. Single housing is necessary because the toxicity of the compound is unknown; therefore the toxic signs expected at each dose are unknown. The SSWP method doses one to three animals at each dose and the doses are often widely spaced. Therefore, pair housing could result in animals being co-housed that may be exhibiting very different toxic signs. Pair-housing may result in healthy animals being co-housed with animals exhibiting seizure activity or with moribund animals. This practice may result in undue stress to the healthy animal or loss of data from the moribund animal if aggression or cannibalism occurs.

V.5.2. Veterinary Medical Care

V.5.2.1. Routine Veterinary Medical Care:

Animals will routinely be observed no less than once daily by assigned veterinary medical personnel for husbandry conditions, humane care, and general health status. IAW current IACUC policy, in the event an animal becomes ill or injured, veterinary or toxicology personnel will contact the AV or his/her designated backup who will determine the appropriate course of action. Animals will be observed daily by study personnel as described in sections V.1.1.2 and V.1.2.2. Animals appearing ill or displaying toxic signs will be assessed for moribundity and early removal from the study as described in section V.4.5.

V.5.2.2. Emergency Veterinary Medical Care:

In the event an animal requires after-hours emergency veterinary care, a veterinarian is available 24 hours a day, 7 days a week. In the case of an emergency health problem, if the PI or co-PI is unavailable or the investigator staff and veterinary staff cannot reach consensus on treatment of a study animal, the veterinarian has the authority to treat the animal, remove it from the experiment, institute appropriate measures to relieve severe pain or distress, or perform euthanasia if necessary. However, all decisions involving the treatment of a study animal in which a consensus cannot be reached will only be made after the veterinarian or designated backup veterinarian has actually observed and examined the animal in question. To facilitate communication, the animal care staff will maintain an emergency contact roster. In an emergency, the animal care staff will phone the numbers (office, home, and mobile) listed for the PI and co-PI. If the PI or co-PI cannot be reached by phone within 15 minutes, then they are considered unavailable.

V.5.3. Environmental Enrichment

V.5.3.1. Enrichment Strategy:

All animals, with the exception of the Acute Study animals following dosing, will be socially housed. All animals will have an enrichment device (e.g., nylabone, rodent retreat) in their cage. All animals on this study will receive the same type of enrichment throughout the study. There will be an environmental enrichment plan posted on the door of the animal room to communicate the enrichment plan to everyone working on the study. This enrichment plan will be in accordance with TOX SOP 033 (USAPHC, 2013h), unless otherwise noted in this section.

Animal Use Protocol: Acute and Subacute Oral Toxicity of Periodate in Rats.

V.5.3.2. Enrichment Restrictions:

The Acute Study animals will be singly housed after dosing (see section V.5.1.3). Food enrichment may not be used due to food consumption monitoring. Rodent retreats may be removed for observation of animals, but will be replaced following observation periods of no more than eight hours.

VI. STUDY PERSONNEL QUALIFICATIONS AND TRAINING:

Personnel on Protocol	Activity to be Performed on Protocol	Formal Training	Qualifications and Experience
Emily Lent	Handling/observations	Rat handling (7/19/07)	Ph.D., Natural Resources and Environmental Studies; M.S., Wildlife Biology 13+ Yrs Animal Research Experience
	Oral Gavage	Rat gavage (7/19/07); Rat oral gavage (03/06/08); Rat oral gavage 14day (05/01/09)	
	Blood collection	Rat bleeding techniques (7/19/07; 4/30/08)	
	CO2 euthanasia	Rat euthanasia via CO2 (7/19/07; 11/18/10)	
Lee Crouse	Handling/observations	Rodent handling techniques (11/21/96); Rat handling (7/19/07)	M.S., Environmental Science 16+ Yrs Animal Research Experience
	Oral Gavage	Rat gavage (07/19/07); Rat oral gavage (05/05/08); rat oral gavage (03/03/08); rat oral gavage 14day (05/01/09)	
	CO2 anesthesia/blood collection	OJT (1996-present)	
	Blood collection	Rat bleeding techniques: cardiac under isoflurane (12/17/08); rat blood collection (7/19/07); Terminal cardiac blood draw (5/1/09)	
	CO2 euthanasia	Rat euthanasia via CO2 (7/19/07; 5/01/09)	
Theresa Hanna	Handling/observations	Animal handling: rat (3/12/92); rat techniques: handling/observations (11/3/08); Rodent small animal handling workshop (2/25/98; 4/2/04; 11/22/05)	ALAT 15+ Yrs Animal Research Experience
	Oral Gavage	Rat oral gavage (10/06/04); Rat oral gavage (11/03/08); rat oral gavage (03/06/08); rat oral gavage 14day (05/01/09); rat oral gavage (06/19/12)	
	Blood collection	Rat techniques: basic bleeding (11/3/08; Rat terminal cardiac blood draw (5/1/09)	
	CO2 euthanasia	Rat euthanasia CO2 (3/27/09); Rat CO2 euthanasia (5/1/09)	
Allison Jackovitz	Handling/observations	Small animal handling workshop (6/4/09); Rat handling (6/12/12)	B.S., Biology 2+ Yrs Animal Research Experience
	Oral Gavage	Rat oral gavage (6/12/12); rat oral gavage (6/19/12)	
	CO2 anesthesia/cardiac blood collection	Cardiac blood collection in rats using CO2 anesthesia (05/02/13; 05/08/13; 05/10/13)	
	CO2 euthanasia	Small animal handling workshop: euthanasia (6/4/09); Rat CO2 euthanasia (6/12/12)	
Alicia Shiflett	Handling/observations	Rat techniques: handling/observations (11/3/08); rat handling (6/12/12)	Associates Degree, Histology/Science 2+ Yrs Animal Research Experience
	Blood collection	Rat techniques: basic bleeding (11/3/08)	
	CO2 euthanasia	Rat CO2 euthanasia (3/27/09)	

Animal Use Protocol: Acute and Subacute Oral Toxicity of Periodate in Rats.

Craig McFarland	Handling/observations	Rat handling techniques (7/19/07); Rodent handling techniques (6/30/11)	Ph.D., DVM, Environmental Toxicology 12+ Yrs Animal Research Experience
	Oral gavage	Rat oral gavage (07/19/07)	
	CO2 anesthesia/cardiac blood collection	Cardiac blood collection in rats using CO2 anesthesia (05/02/13; 05/08/13; 05/10/13)	
	Blood collection	Rat techniques: blood collection (7/19/07)	
	CO2 euthanasia	Rat techniques: euthanasia (7/19/07); Rat euthanasia (10/16/07)	
Art O'Neill	Handling/observations	Inhalation testing experience (memo from DuPont dated 10/08)	B.S., Biology LATG 30+ Yrs Animal Research Experience
	CO2 euthanasia	Inhalation testing experience (memo from DuPont dated 10/08)	
William Eck	Handling/observations	Rat handling (7/19/07): Small animal handling workshop (5/28/09)	Ph.D., Biochemistry 8+ Yrs Animal Research Experience
	Oral gavage	Rat oral gavage (07/19/07)	
	Blood collection	Rat techniques: blood collection (7/19/07); Small animal handling workshop: IC bleed in rats (5/28/09)	
	CO2 euthanasia	Rat techniques: euthanasia (7/19/07); Small animal handling workshop: CO2 euthanasia (5/28/09)	
Emily Reinke (nee Terry)	Handling/observations	Rat handling (6/12/12)	M.S. Animal Science 4 Yrs Animal Research Experience
	Oral gavage	Rat oral gavage (6/12/12)	
	CO2 euthanasia	Rat CO2 euthanasia (6/12/12)	

VII. BIOHAZARD/SAFETY: Risks associated with this protocol include bites/scratches/needle sticks, transmission of zoonotic diseases, and the development of animal allergies. To minimize risk, appropriate handling techniques will be used and appropriate personal protective equipment (PPE) will be worn for all animal handling work. This includes (but may not be limited to) facemask, gloves, and disposable lab coat. Personnel will wash their hands upon completion of animal work. Applicable current PHC regulations and TOX SOPs(USACHPPM 385-5, OHS of Animal Users and TOX SOP 046) will be followed (USACHPPM, 2007, USAPHC, 2013i). These documents specify hazardous waste disposal, bite/scratch procedures, and zoonotic disease prevention. A sharps container will be present at all times when using sharps and needles will not be recapped after entering animal tissue.

VIII. ENCLOSURES:

A. References

Animal Use Protocol: Acute and Subacute Oral Toxicity of Periodate in Rats.

IX. ASSURANCES: The law specifically requires several written assurances from the Principal Investigator. Please read and sign the assurances as indicated below.

IX.1. As the Principal Investigator on this protocol, I acknowledge my responsibilities and provide assurances for the following:

A. Animal Use: The animals authorized for use in this protocol will be used only in the activities and in the manner described herein, unless a modification is specifically approved by the IACUC prior to its implementation.

B. Duplication of Effort: I have made every effort to ensure that this protocol is not an unnecessary duplication of previous experiments.

C. Statistical Assurance: I assure that I have consulted with a qualified individual who evaluated the experimental design with respect to the statistical analysis, and that the minimum number of animals needed for scientific validity will be used.

D. Biohazard/Safety: I have taken into consideration and made the proper coordination regarding all applicable rules and regulations concerning radiation protection, biosafety, recombinant issues, and so forth, in the preparation of this protocol.

E. Training: I verify that the personnel performing the animal procedures / manipulations / observations described in this protocol are technically competent and have been properly trained to ensure that no unnecessary pain or distress will be caused to the animals as a result of the procedures / manipulations.

F. Responsibility: I acknowledge the inherent moral, ethical and administrative obligations associated with the performance of this animal use protocol, and I assure that all individuals associated with this project will demonstrate a concern for the health, comfort, welfare, and well-being of the research animals. Additionally, I pledge to conduct this study in the spirit of the fourth "R", namely, "Responsibility," which the DOD has embraced for implementing animal use alternatives where feasible and conducting humane and lawful research.

G. Scientific Review: This proposed animal use protocol has received appropriate peer scientific review and is consistent with good scientific research practice.

H. Painful Procedures: *(Applicable if the research being conducted has the potential to cause more than momentary or slight pain or distress even if an anesthetic or analgesic is used to relieve the pain and/or distress.)*

I am conducting biomedical experiments, which may potentially cause more than momentary or slight pain or distress to animals. This potential pain and/or distress WILL / WILL NOT (circle one or both, if applicable) be relieved with the use of anesthetics, analgesics and/or tranquilizers. I have considered alternatives to such procedures; however, I have determined that alternative procedures are not available to accomplish the objectives of this proposed experiment.

Emily May Lent
(PRINT) First name/MI, Last name of Principal Investigator

Emily May Lent
(Signature)

6/24/13
(Date)

Animal Use Protocol: Acute and Subacute Oral Toxicity of Periodate in Rats.

IX.2. As the Primary Co-Investigator on this protocol, I provide the following assurances:

A. Animal Use: The animals authorized for use in this protocol will be used only in the activities and in the manner described herein, unless a modification is specifically approved by the IACUC prior to its implementation.

B. Authority: I understand that, as the Primary Co-Investigator, I am authorized and responsible for performing all procedures and manipulations as assigned to the SD/PI in the SD/PI's absence. This includes euthanasia of distressed animals.

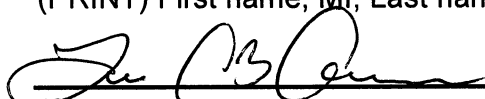
C. Training: I verify that I am technically competent and have been properly trained to ensure that no unnecessary pain or distress will be caused to the animals as a result of the procedures/manipulations.

D. Responsibility: I acknowledge the inherent moral and administrative obligations associated with the performance of this animal use protocol, and I assure that I will demonstrate a concern for the health, comfort, welfare, and well-being of the research animals. Additionally, I pledge to conduct this study in the spirit of the fourth "R", namely "Responsibility," which the DOD has embraced for implementing animal use alternatives where feasible, and conducting humane and lawful research.

E. Painful Procedures: I am conducting biomedical experiments, which may potentially cause more than momentary or slight pain or distress to animals. This potential pain and/or distress WILL or WILL NOT (circle one or both, if applicable) be relieved with the use of anesthetics, analgesics and/or tranquilizers. I have considered alternatives to such procedures; however, I have determined that alternative procedures are not available to accomplish the objectives of this proposed experiment.

Lee CB Crouse

(PRINT) First name, MI, Last name of Primary Co-Investigator


(Signature)

10-24-13
(Date)

Animal Use Protocol: Acute and Subacute Oral Toxicity of Periodate in Rats.

IX.2. As a Co-Investigator on this protocol, I provide the following assurances:

A. Animal Use: The animals authorized for use in this protocol will be used only in the activities and in the manner described herein, unless a modification is specifically approved by the IACUC prior to its implementation.

B. Authority: I understand that, as a Co-Investigator, I am authorized, responsible for, and willing to perform all procedures and manipulations as assigned to me by the SD/PI.

C. Training: I verify that I am technically competent and have been or will be properly trained to ensure that no unnecessary pain or distress will be caused to the animals as a result of the assigned procedures/manipulations performed by me.

D. Responsibility: I acknowledge the inherent moral and administrative obligations associated with the performance of this animal use protocol, and I assure that I will demonstrate a concern for the health, comfort, welfare, and well-being of the research animals. Additionally, I pledge to participate in this study in the spirit of the fourth "R", namely "Responsibility," which the DOD has embraced for implementing animal use alternatives where feasible, and conducting humane and lawful research.

E. Painful Procedures: I am participating in biomedical experiments, which may potentially cause more than momentary or slight pain or distress to animals. I will follow the direction of the SD/PI relative to potential pain and/or distress and relief by use of anesthetics, analgesics, and/or tranquilizers.

William S. Eick

24. June 2013

(PRINT)

(SIGNATURE)

(DATE)

First name, MI, Last name of Co-Investigator

(PRINT)

(SIGNATURE)

(DATE)

First name, MI, Last name of Co-Investigator

(PRINT)

(SIGNATURE)

(DATE)

First name, MI, Last name of Co-Investigator

(PRINT)

(SIGNATURE)

(DATE)

First name, MI, Last name of Co-Investigator

APPENDIX A

REFERENCES

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USAPHC 2013b. TOX SOP 013.000, Cell-Dyn Hematology Analyzer. Aberdeen Proving Ground, Maryland.

USAPHC 2013c. TOX SOP 020.000, TOSOH Automated Enzyme Immunoassay System. Aberdeen Proving Ground, Maryland.

USAPHC 2013d. TOX SOP 022.000, Animal Health Technician Duties in Animal Holding Rooms. Aberdeen Proving Ground, Maryland.

USAPHC 2013e. TOX SOP 024.000, Individual Animal Identification. Aberdeen Proving Ground, Maryland.

USAPHC 2013f. TOX SOP 026.000, Test System Observations. Aberdeen Proving Ground, Maryland.

USAPHC 2013g. TOX SOP 027.000, Animal Euthanasia. Aberdeen Proving Ground,

Animal Use Protocol: Acute and Subacute Oral Toxicity of Periodate in Rats.

Maryland.

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USAPHC 2013i. TOX SOP 046.000, Health and Safety of Laboratory Personnel. Aberdeen Proving Ground, Maryland.





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PROTOCOL REVIEW, SUPPORT, APPROVAL SHEET

PROTOCOL NUMBER: - 30 - 13-06-01 <small>SUB-JONO TEST TYPE IACUC NUMBER</small>		TITLE: Acute and Subacute Oral Toxicity of Periodate in Rats	
1. SCIENTIFIC MERIT (PEER REVIEW)			
1a. Printed Name (First, MI, Last) William Eck	1b. Title Biologist	1c. Signature ECK.WILLIAM.S.1145749839	1d. Date (yyyy/mm/dd) 20130523
2. DIRECTOR			
2a. Printed Name (First, MI, Last) Mark S. Johnson	2b. Title Portfolio Director, Toxicology	2c. Signature  Click to Approve	2d. Date (yyyy/mm/dd)
3. PROGRAM MANAGER			
3a. Printed Name (First, MI, Last) Arthur J. O'Neill	3b. Title Biologist Program Manager, TEP (Acting)	3c. Signature  Click to Approve	3d. Date (yyyy/mm/dd)
4. ATTENDING VETERINARIAN			
4a. Printed Name (First, MI, Last) Dawn Fitzhugh	4b. Title LTC, VC Attending Veterinarian	4c. Signature FITZHUGH.DAWN.CATHERINE.1036926127	4d. Date (yyyy/mm/dd) 20130523
5. ANALYTICAL CHEMISTRY (If Applicable)			
5a. Printed Name (First, MI, Last) David Morrow	5b. Title Chief, Laboratory Consultants Division	5c. Signature  Click to Approve	5d. Date (yyyy/mm/dd)
6. SAFETY MANAGER			
6a. Printed Name (First, MI, Last) Roy Valiant	6b. Title Safety Manager	6c. Signature  Click to Approve	6d. Date (yyyy/mm/dd)
7. STATISTICIAN (If Applicable)			
7a. Printed Name (First, MI, Last) Karen Deaver	7b. Title Statistician	7c. Signature DEAVER.KAREN.DEVILBISS.1400519672	7d. Date (yyyy/mm/dd) 20130523

PROTOCOL NUMBER: - 30 - 13-06-01 SUB-JONO TEST TYPE IACUC NUMBER		TITLE: Acute and Subacute Oral Toxicity of Periodate in Rats	
8. SIO-QAT (GLP COMPLIANCE AND QA SUPPORT)			
8a. Printed Name (First, MI, Last) Michael P. Kefauver	8b. Title Quality Assurance Specialist, USAPHC Quality Systems Office	8c. Signature  Click to Approve	8d. Date (yyyy/mm/dd)
9. CHAIRMAN, IACUC			
9a. Printed Name (First, MI, Last) Kristin Newkirk	9b. Title Chairman, IACUC	9c. Signature NEWKIRK.KRISTIN.TORELL.1014786895 ✓	9d. Date (yyyy/mm/dd) 20130625
10. INSTITUTIONAL OFFICIAL			
10a. Printed Name (First, MI, Last) John Resta	10b. Title Director, IPH	10c. Signature RESTA.JOHN.J.1229129305 ✓	10d. Date (yyyy/mm/dd) 20130626
11. STUDY DIRECTOR/PRINCIPAL INVESTIGATOR			
11a. Printed Name (First, MI, Last) Emily May Lent	11b. Title Toxicologist	11c. Signature LENT.EMILY.MAY.1296114371 ✓	11d. Date (yyyy/mm/dd) 20130627
12. OTHER ORGANIZATION(S) PROVIDING SUPPORT (AS NEEDED):			
12a. Printed Name (First, MI, Last)	12b. Title	12c. Signature	12d. Date (yyyy/mm/dd)
13. STUDY SPONSOR:			
13a. Printed Name (First, MI, Last) Mark S. Johnson for Kimberly A. Watts	13b. Title Deputy Program Manager, Environmental Acquisition & Logistics Sustainment Program	13c. Signature	13d. Date (yyyy/mm/dd)

USACHPPM PROTOCOL MODIFICATION

For use of this form, see DTOX SOP 085

1. DATE: (YYYY/MM/DD) 2013/08/20

2. PROTOCOL NUMBER: 30-13-06-01

3. MODIFICATION#: 1

4. PROTOCOL TITLE: Acute and Subacute Oral Toxicity of Periodate in Rats

5. STUDY DIRECTOR/PRINCIPAL INVESTIGATOR:

Emily May Lent

6. WORK PHONE:

436-7749

7. OFFICE SYMBOL:

MCHB-IP-TTE

SECTION I. PREVIOUSLY APPROVED AND CURRENTLY IN USE PROTOCOL MODIFICATIONS:

1. MODIFICATION NUMBER	2. SHORT DESCRIPTION OF PRIOR APPROVED MODIFICATION(S)	3. NO. & SPECIES OF ANIMAL REQUESTED	4. APPROVED DATE (XX XXX XXXX)

SECTION II. CHANGE IN TOTAL # OF ANIMALS USED AND/OR CHANGE IN USDA PAIN CATEGORY

1a. CHANGE: INCREASE TOTAL APPROVED ANIMALS BY: 0

1b. N/A ☒

2. ORIGINAL PROTOCOL TOTAL: 247

3. PROTOCOL TOTAL AFTER MODIFICATION: 247

2a. USDA pain cat:

B: 0

C: 84

D: 110

E: 53

3a. USDA pain cat:

B: 0

C: 84

D: 110

E: 53

4. Yes No

////////////////////////////////////

☒ ☐

Modification requires specific changes or additions to the experimental design of the protocol. (Section V.I. of the template.)

☒ ☐

Modification requires changes to the technical methods, i.e., procedures, routes of administration, biosample collection, etc. (Section V.4. of the protocol template.) Indicate training of personnel for new methods, procedures being used.

☐ ☒

Modification requires additions or changes in personnel performing procedures. (Section VI of the protocol template.) Include training and qualification information and tasks that each individual will be performing. If changing the Study Director/PI, a signed Assurance Statement needs to be submitted with the modifications.

PROTOCOL
Page, paragraph,
section

SECTION III. MODIFICATION/JUSTIFICATION

Explain the modification indicated above in the area below. Indicate any changes to the 3R's (Refinement, Reduction, Replacement) resulting from changes in number of animals

Page 9
V.1.2. Subacute
Study

1. MODIFICATION:

ADD: Urinalysis (using urine collected using metabolism cages) will be performed on rats surviving to the study endpoint. Urinalysis may also be performed on free-catch urine collected, when possible, from rats determined to be moribund (as described in section V.4.4.3.2.). Urinalysis procedures will follow those outlined in TOX SOP 003.000.

1a. JUSTIFICATION/REASON:

Clinical observations of rats on study (pink/brown urine) and observations during necropsies conducted on moribund animals indicate potential kidney effects. Urinalysis will provide additional data to determine the nature and extent of the kidney effects.

PROTOCOL Page, paragraph, section	Explain the modification indicated above in the area below. Indicate any changes to the 3R's (Refinement, Reduction, Replacement) resulting from changes in number of animals used.	
Page 17 V 4 4 3 Biosamples V 4 4 3 2 Urinalysis	2. MODIFICATION: ADD SECTION V 4 4 3 2 Urinalysis Rats will be individually placed in metabolism cages capable of separating urine and feces for 15-16 hours prior to scheduled necropsy for collection of urine samples. Urine voided by the rat while in the cage will passively collect in the urine collection tube and will be recorded as a volume per sample time. Urine will be removed from the collection cups as soon as possible at the conclusion of the sample collection period and placed in labeled, clear, conical tubes. Free-catch urine may also be collected, when possible, from rats determined to be moribund by attempting to catch urine in sample tubes when rats are observed to be urinating. Urinalysis will be conducted IAW TOX SOP 003 000. 2a JUSTIFICATION/REASON: Clinical observations of rats on study (pink/brown urine) and observations during necropsies conducted on moribund animals indicate potential kidney effects. Urinalysis will provide additional data to determine the nature and extent of the kidney effects.	
Page 19 V 5 1 2 Special Husbandry Provisions	3. MODIFICATION: ADD Rats will be individually placed in metabolism cages overnight (approximately 15-16 hours) prior to scheduled necropsy for collection of urine. Study staff will place the rats into the metabolism cages. Feed will be removed to eliminate sample contamination as well as to fast the rat prior to necropsy (as described section V 5 1 2). Water will be provided ad libitum. Animals will be returned to their home cages (return to the pair housed mate) the morning of necropsy and will continue to be fasted in their home cages until the time they are necropsied. Fasting will not exceed 24 hours. 3a JUSTIFICATION/REASON: Clinical observations of rats on study (pink/brown urine) and observations during necropsies conducted on moribund animals indicate potential kidney effects. Urinalysis will provide additional data to determine the nature and extent of the kidney effects.	
	4. MODIFICATION: 4a. JUSTIFICATION/REASON:	
Continued on next page YES NO <input checked="" type="checkbox"/>		
SECTION IV. SIGNATURES AND DATES		
1 STUDY DIRECTOR: (Printed Name) Emily May Leat	Signature Emily May Leat	DATE (yyyy/mm/dd) 2013-08-23
2 PROGRAM MANAGER: (Printed Name) ARTHUR J. O'NEILL	Signature Arthur J. O'Neill	DATE (yyyy/mm/dd) 2013-08-23
3 ATTENDING VETERINARIAN: (Printed Name) Richard J Probst	Signature Rick J Probst	DATE (yyyy/mm/dd) 2013-08-22
4 CHPPM SAFETY OFFICER/OCG HEALTH REP (IF APPLICABLE)	Signature	DATE (yyyy/mm/dd)
5 CHAIR, IACUC OR QA (If no animal related changes): (Printed Name) LAWRENCE TANNENBAUM	APPROVED / REVIEWED <input checked="" type="checkbox"/> YES NO Signature Lawrence Tannenbaum	DATE (yyyy/mm/dd) 2013-08-23

USACHPPM PROTOCOL MODIFICATION

For use of this form, see DTOX SOP 085

MPK
10/1/13
ME
+ GLP-1

1. DATE: (YYYY/MM/DD) 2013/09/30

2. PROTOCOL NUMBER: 30-13-06-01

3. MODIFICATION#:

+ GLP-1

4. PROTOCOL TITLE: Acute and Subacute Oral Toxicity of Periodate in Rats

5. STUDY DIRECTOR/PRINCIPAL INVESTIGATOR:

Emily May Lent

6. WORK PHONE:

410-436-7749

7. OFFICE SYMBOL:

MCHB-IP-TTE

SECTION I. PREVIOUSLY APPROVED AND CURRENTLY IN USE PROTOCOL MODIFICATIONS:

1. MODIFICATION NUMBER	2. SHORT DESCRIPTION OF PRIOR APPROVED MODIFICATION(S)	3. NO. & SPECIES OF ANIMAL REQUESTED	4. APPROVED DATE (XX XXX XXXX)

SECTION II. CHANGE IN TOTAL # OF ANIMALS USED AND/OR CHANGE IN USDA PAIN CATEGORY

1a. CHANGE: INCREASE TOTAL APPROVED ANIMALS BY:

1b. N/A ☒

2. ORIGINAL PROTOCOL TOTAL: 247

3. PROTOCOL TOTAL AFTER MODIFICATION: 247

2a. USDA pain cat:

B: 0

C: 84

D: 110

E: 53

3a. USDA pain cat:

B: 0

C: 84

D: 110

E: 53

4. Yes No



Modification requires specific changes or additions to the experimental design of the protocol. (Section V.I. of the template.)



Modification requires changes to the technical methods, i.e., procedures, routes of administration, biosample collection, etc. (Section V.4. of the protocol template.) Indicate training of personnel for new methods, procedures being used.



Modification requires additions or changes in personnel performing procedures. (Section VI of the protocol template.) Include training and qualification information and tasks that each individual will be performing. If changing the Study Director/PI, a signed Assurance Statement needs to be submitted with the modifications.

PROTOCOL
Page, paragraph,
section

SECTION III. MODIFICATION/JUSTIFICATION

Explain the modification indicated above in the area below. Indicate any changes to the 3R's (Refinement, Reduction, Replacement) resulting from changes in number of animals

Page 11, Section
V.1.2.4.3.
Histopathology

1. MODIFICATION:

ADD: Thyroid sections will be subjectively evaluated for follicular cell height and colloid area using a five point grading scale (1 = shortest/smallest; 5 = tallest/largest) and any abnormalities/lesions noted. A minimum of two sections of each of the two lobes of the thyroid will be evaluated, when available. Histopathological examination of ovaries may include an evaluation of follicular development, including enumeration of primordial, primary, and tertiary/antral follicles, as well as corpora lutea. Changes in folliculogenesis will be determined in addition to any abnormalities/lesions, such as ovarian atrophy. The ovary may be trimmed until the outer third has been removed and a clear rim of follicles/corpora lutea established around the central stroma. The ovary will be sectioned at 5 µm thickness and a total of 5 random sections per ovary evaluated.

1a. JUSTIFICATION/REASON:

More detailed/quantitative histological methods for the thyroid and ovaries are needed to help elucidate potential effects on these probable/apparent target tissues.

PROTOCOL Page, paragraph, section	Explain the modification indicated above in the area below. Indicate any changes to the 3R's (Refinement, Reduction, Replacement) resulting from changes in number of animals used.
	2. MODIFICATION:
	2a. JUSTIFICATION/REASON:
	3. MODIFICATION:
	3a. JUSTIFICATION/REASON:
	4. MODIFICATION:
	4a. JUSTIFICATION/REASON:

Continued on next page YES ☐ NO ☒

SECTION IV. SIGNATURES AND DATES

1. STUDY DIRECTOR: (Printed Name) <i>Emily May Lent</i>	Signature <i>Emily May Lent</i>	DATE: (yyyy/mm/dd) <i>2013/09/30</i>
2. PROGRAM MANAGER:: (Printed Name) <i>ARTHUR J. O'NEILL</i>	Signature <i>Arthur J. O'Neill</i>	DATE: (yyyy/mm/dd) <i>2013/09/30</i>
3. ATTENDING VETERINARIAN: (Printed Name)	Signature	DATE: (yyyy/mm/dd)
4. CHPPM SAFETY OFFICER/OCC HEALTH REP: (IF APPLICABLE)	Signature	DATE: (yyyy/mm/dd)
5. CHAIR, IACUC OR QA (If no animal related changes): (Printed Name) <i>Michael P. Kefauver</i> <i>MICHAEL P. KEFAUVER</i>	APPROVED / REVIEWED YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> Signature <i>Michael P. Kefauver</i>	DATE: (yyyy/mm/dd) <i>2013/09/30</i>